Facioscapulohumeral Muscular Dystrophy:

Making an Informed Choice About Genetic Testing

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http://www.rehabinfo.net
and the author's website:
http://depts.washington.edu/neurogen

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This booklet provides information about facioscapulohumeral muscular dystrophy (FSHD) and genetic testing for FSHD. Facioscapulohumeral dystrophy is an inherited disorder of muscle function. It is characterized by weakness of specific muscles in the face, shoulder, upper arm, hip and lower leg. Facioscapulohumeral dystrophy is one of the most common forms of inherited muscle disease; it is estimated that one person in every 20,000 is affected with FSHD. facioscapulohumeral dystrophy is an extremely variable condition, even within families. Genetic testing is available for FSHD. The decision to be tested is a personal one, and each person must make his or her own informed choice about testing.

SYMPTOMS OF FACIOSCAPULOHUMERAL DYSTROPHY

The degree of muscle weakness in facioscapulohumeral dystrophy varies greatly from person to person. In its most severe form, infants with FSHD can have extreme muscle weakness (infantile FSHD). In contrast, FSHD can be so mild in adults that they may not be aware they are affected until a relative with more symptoms comes to medical attention. Facioscapulohumeral

dystrophy affects males and females equally. By the age of 20 years, almost all affected persons have some degree of muscle weakness due to atrophy or shrinkage of the muscles (See Figure 1). The weakness is often most evident in the muscles of the face, and results in difficulty with smiling and whistling, and reduced facial expression. However, some people with FSHD have little or no facial weakness. Other commonly affected muscles are those of the shoulder, causing the scapula (shoulder blade) to protrude from the

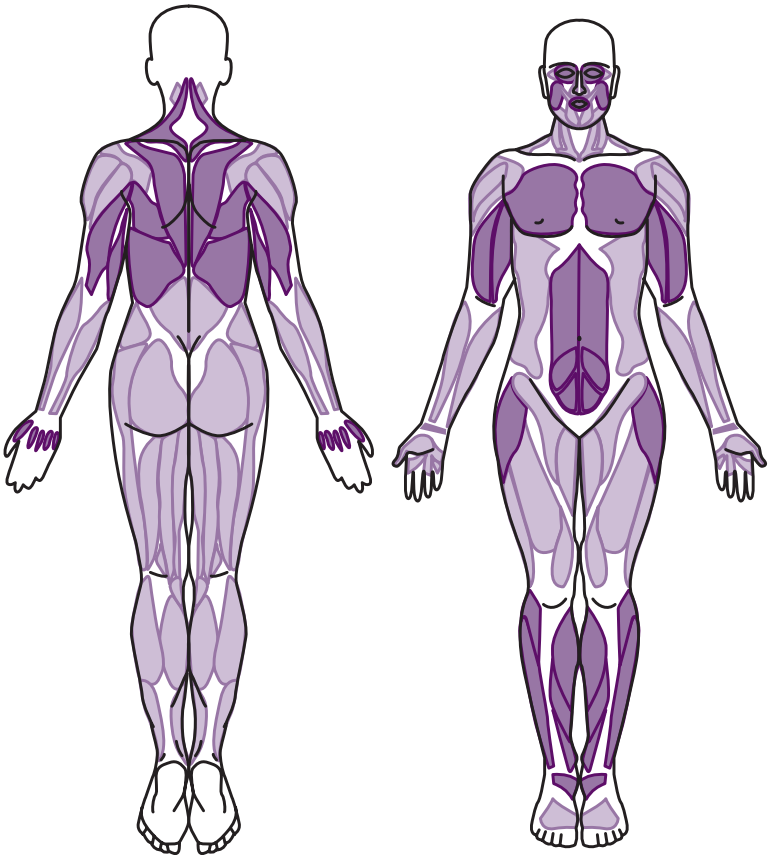

Figure 1. Dark shading indicates muscles most often affected in facioscapulohumeral dystrophy.

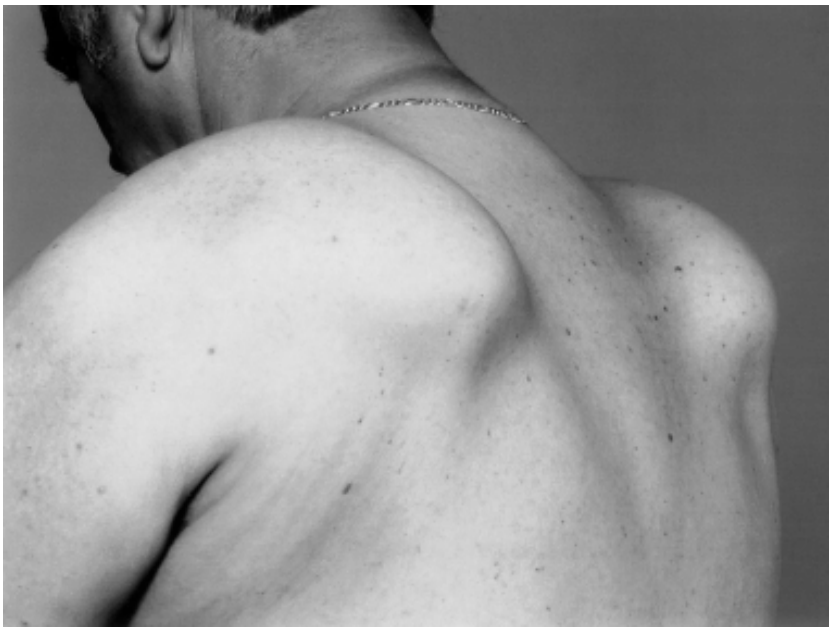

Figure 2. “Winging of the scapula” caused by weakness of the shoulder muscles

back (“winging of the scapula”, see Figure 2). Muscles of the hip and lower leg can become weak and lead to difficulty with walking. Pectoral muscles of the chest and abdominal muscles may also become weak. The muscles involved with breathing and swallowing are not usually affected, but can be in severe cases. For reasons that are not known, the muscle weakness is often more noticeable on one side of the body than the other.

In most cases, FSHD is slowly progressive, with weakness increasing over a period of years. Some people experience relatively rapid progression of weakness followed by long periods of stability. In a minority of persons with FSHD, the muscle weakness can continue to the point where they have difficulty walking and need a wheelchair. The extent to which muscle weakness will affect a person’s ability to function is variable and unpredictable. At this time, there is no treatment or cure that can prevent the symptoms of FSHD.

Most people with facioscapulohumeral dystrophy will eventually develop high-frequency hearing loss. This hearing loss is not usually noticeable, and can only be detected with a hearing exam called an audiogram. Abnormalities of heart rhythm, called arrhythmias, can occur in persons with FSHD. With few exceptions, these arrhythmias do not cause any medical problems. Another finding seen in some but not all persons with FSHD are abnormalities in the blood vessels of the eye that rarely cause problems with vision.

INHERITANCE OF FSHD

Facioscapulohumeral dystrophy is inherited in an autosomal dominant pattern (See Figures 3 and 4). This means each son or daughter of a person with FSHD has a 1 in 2, or 50% chance of inheriting the condition. At this time, the specific gene for FSHD has not been found.

Genes are the basic units of heredity, and contain the set of instructions that determine how the body grows and develops. Genes are composed of DNA (deoxyribonucleic acid). It is estimated that every cell in a person's body contains between 30,000 to 40,000 genes. Genes are packaged on chromosomes – the threadlike structures within cells that are visible with a microscope (genes

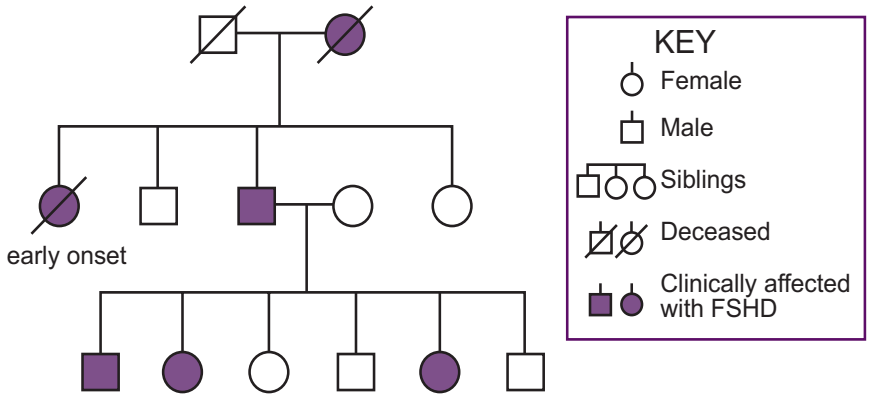

Figure 3. Family tree (pedigree) of a family with facioscapulohumeral dystrophy showing autosomal dominant inheritance.

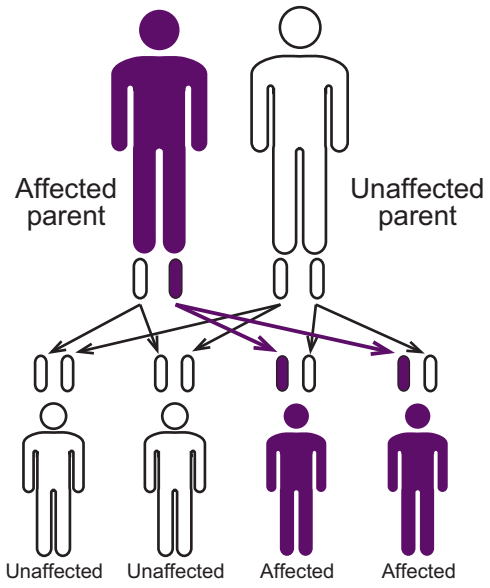

Figure 4. Diagram of autosomal dominant inheritance. Each child has a 50% chance of inheriting FSHD from an affected parent.

cannot be seen with a microscope). Each person inherits half of their chromosomes from their father, and half from their mother. Every person has 23 pairs of chromosomes, which contain two copies of each gene. Current research suggests that the gene for FSHD is located on chromosome number 4.

Genetic testing is available for FSHD. The genetic test measures the size of a region of DNA that is missing or deleted in persons with FSHD. It is not yet known how this deletion causes FSHD, because no genes are known to be in the DNA region that is deleted. One theory is that the deletion interacts with a gene or genes on chromosome 4. When the DNA region is deleted, a gene may not function properly, leading to muscle weakness. About 95% of people who have been diagnosed with FSHD will have a deletion detected by genetic testing.

In facioscapulohumeral dystrophy, there is an association between the size of the deletion, age of symptom onset and the severity of symptoms. In general, the larger the size of the deletion,

the younger the age at which a person will develop symptoms of FSHD and the more severe the symptoms will be. On the other hand, the deletion size cannot be used to predict the age when a person will develop symptoms, or the rate of symptom progression. The largest deletions are seen in infantile FSHD.

In some cases, a person can be the first in a family to have FSHD. This can happen in one of four ways:

(1) a parent had a very mild case of FSHD that was never diagnosed.

(2) a parent had the deletion but never developed symptoms of FSHD (see section on penetrance for explanation).

(3) a deletion occurred in the sperm or egg that formed the person (new mutation). If a person has FSHD because of a new mutation, then family members (other than his or her children) are not at increased risk to have the condition. Children of a person with a new mutation have a 50% chance of inheriting FSHD.

(4) a parent has germline mosaicism. Mosaicism means that not all of the cells in a person's body have the same genetic content, and germline refers to the germ cells – the cells that form eggs in women and sperm in men. Mosaicism happens when a new mutation (deletion) occurs in a single cell early in the growth of a pregnancy. This cell then divides many times, with the deletion present in all the cells that came from this one cell. As a result, not every cell of the body contains the deletion. The effect of mosaicism is that a person may not show signs of FSHD, but be at risk to pass on the condition to his or her children if the germ cells contain the deletion. The exact risk of passing on FSHD is variable in cases of germline mosaicism, but can be as high as 50%. Germline mosaicism is uncommon, but is known to happen in a number of genetic conditions including FSHD.

With the availability of genetic testing, it has been discovered that a small number of families with FSHD do not have a deletion. For this reason, researchers think there is more than one genetic

cause for FSHD, although no other gene or associated deletion has been found. In these rare families, genetic testing is not useful for making the diagnosis of FSHD.

Penetrance

The term penetrance refers to the proportion of persons with a deletion for FSHD who will actually develop symptoms of the condition. In FSHD, penetrance is high, meaning that almost everyone with a deletion will develop at least mild symptoms of FSHD at some point in their lifetime. In some cases, a person's symptoms can be so mild that they are never diagnosed. In addition, up to 5% of persons with a deletion will not develop any symptoms (non-penetrance). Children of these persons remain at 50% risk to inherit FSHD. Genetic testing is the best way to clarify which family members are at risk for FSHD.

DNA TESTING

Genetic testing is available to determine whether or not a person has inherited the DNA deletion that is associated with FSHD. The testing can be done on a blood or tissue sample. Testing for FSHD usually takes between 2-6 weeks for results.

There are three possible outcomes from DNA testing:

Negative/Normal

This result means that the person being tested has not inherited FSHD. The genetic testing shows that a deletion is not present. The accuracy of this result is close to 100%. A person can appear to have FSHD and still have a negative test result. This can happen if the person has muscle weakness from another cause, or in rare cases where a person has FSHD that is not associated with the deletion. A negative result is most meaningful if the diagnosis of FSHD has been confirmed in an affected relative through genetic testing.

Positive

This result means that a person has inherited a DNA deletion for FSHD. The accuracy of this result is close to 100%. A positive result does not necessarily mean that a person has any physical signs of FSHD, nor does it indicate at what age a person will begin to show signs of FSHD. A positive result usually means that at some point in that person's lifetime, he or she will develop at least mild

signs of FSHD. However, there is variability in the severity of symptoms and the rate of symptom progression, as well as the age of disease onset even within the same family. Persons with symptoms of FSHD should be examined by a neurologist who can confirm the diagnosis and provide continuing medical support and care.

Uncertain

There is an area of uncertainty or "gray range" in FSHD genetic testing. Usually, the testing provides a clear answer about whether or not a person has inherited FSHD. However, in some cases the deletion is so small that it is unclear if it is associated with symptoms of FSHD. For example, If a person with symptoms characteristic of FSHD has a deletion size in the gray range, then it is likely that the small deletion is associated with the symptoms. In contrast, if a person has an unusual pattern of muscle weakness that may or may not be due to FSHD, caution must be used when interpreting deletion sizes in the gray range.

TESTING PROCESS

Genetic testing for FSHD involves more than providing a blood sample.

Symptomatic and asymptomatic testing

There is a big difference between genetic testing done to find the cause of muscle weakness in a person (symptomatic testing) versus someone who is at risk for FSHD and has no symptoms of the condition (asymptomatic testing). For a person with symptoms, testing for FSHD is part of a diagnostic evaluation. If the test is positive, it provides a diagnosis for the person, as well as an explanation for the symptoms. Often the most difficult thing for a symptomatic person who has a positive test result is learning that his or her children, siblings and other family members are now at risk for FSHD. For a person without symptoms, there are many issues to think about prior to having testing. The following information is most applicable to at risk persons considering asymptomatic testing for FSHD, but may also be useful for those with symptoms of FSHD who are undergoing testing.

Genetic counseling

Genetic counseling is an essential part of the asymptomatic testing process. Genetic counseling involves providing information about the implications of the testing by someone with expertise in genetic testing such as a genetic counselor or medical geneticist. A neurological exam is done as part of the testing process to find out if a person is showing any signs of FSHD. Persons with symptoms may discuss testing with a neurologist or a genetics professional.

Confirmation of FSHD in the family

It is very important to confirm the diagnosis of FSHD in the family. Often medical records on affected family members are requested. It is most useful to perform the genetic test on an affected family member to confirm the presence of a deletion for FSHD. Other muscle diseases may mimic FSHD, but persons with other diseases will have a normal genetic test for FSHD.

Do you think you have inherited facioscapulohumeral dystrophy?

Honestly considering your feelings about whether or not you believe you have or will develop FSHD is important. It can be more difficult to deal with the test results if the results are the opposite of your inner feelings. Often people can have signs of FSHD without knowing it. Many people with mild FSHD never come to medical attention.

Support person

The decision of whether or not to have testing for FSHD can be stressful. Waiting for the results can also be stressful. The results, even “good news,” can take time for adjustment. Having a support person (such as a close friend or spouse) who is able to be present at all appointments is helpful. This person can be a second set of ears as well as a sounding board to talk through feelings about testing, and provide support after the test results are given.

Cost

Costs will vary among testing programs. Usually the cost of testing (DNA blood test, pre- and post-test counseling, and neurological examination) is under $1,200. Many insurance companies will cover the cost of this testing.

THE DECISION TO BE TESTED

The decision to be tested is very personal and may be one of the most important decisions you ever face. Members of the same family may have different feelings about testing. It is important to respect each person's feelings. For at-risk persons who do not have symptoms of FSHD, there can be both medical and psychological benefits to having testing. The test results also have important implications for many life decisions. The following are just some of the issues to consider in the decision to have symptomatic testing:

Timing of testing

The process of being tested for FSHD and dealing with the results may be stressful and disruptive to a person's life. It is best to choose a time to be tested when complicating factors from the outside are at a minimum. For example, the middle of a divorce or break-up of a relationship, or a stressful time at school or work is not a good time to be tested. Testing at a time of celebration may not be optimal, for example, directly before or after marriage, or in the middle of important holidays.

It is easy to become consumed with thinking about testing for FSHD. It is useful to make a decision about whether or not to be tested even if the decision is not a yes or no answer. For example, deciding not to be tested for a certain period of time ("next year", or "after I turn 30"), can help you put this aspect of FSHD aside for a period of time until you are ready to readdress testing issues in the future.

Disclosure of results

If you decide to be tested it is important to plan to whom you will tell your results and when. Will you tell them on the same day that you are given your results? Exactly how and when do you plan to tell them? What if you change your mind and do not want them to know quite yet or at all? Planning what you will do the day you are given the results can be helpful. Will you go directly home, and

who will be there? Will you take some time off work or from family responsibilities?

Effect on relationships

Spouse - Is this person supportive of your decision to be tested or do they have a conflict with your decision? Is he or she pushing you to have testing? Have you discussed decisions that affect you as a couple that you might make differently depending on your test results, for example decisions to have children, retirement and long-term care issues? Many people who are at risk for FSHD fear abandonment by their spouse or significant other when they develop signs of the condition. Have you discussed this or other fears with your partner?

Child – Do your children know about FSHD? Are they pushing you to have testing or are you involving them in your decision making? Will you tell them your results? If yes, how and when will you tell them?

Extended family – How do you perceive the results of the testing will impact your interactions with your brothers and sisters, your parents and extended family? If the results show you have inherited the FSHD deletion, will this impact how you feel about your affected relatives, for example, feeling closer or more distant from them? If you do not have the FSHD deletion you may experience "survivor guilt", meaning that you wonder why you have escaped this disease whereas others in your family have been less fortunate. A person given a normal result may also feel an increased responsibility to take care of affected family members that he or she may not have felt before testing. Who, if anyone, in your family do you plan to tell your results? How would you tell each of them (by phone or letter, at a family meeting)?

Friends – Are there people in your life that you feel you can talk to about FSHD and your decision regarding testing? Have you been through difficult periods in your life with them before? In what ways were they supportive to you?

Professional support

If you have used professional support services such as a therapist, psychologist, religious professional or psychiatrist during a difficult time in the past, it may be helpful to discuss your decision about testing with this person. This is particularly important if you have had prior problems with depression, anxiety or stress.

Family planning

If you have not yet started a family, or are thinking about having more children, it is important to consider how the test result may impact your family planning decisions. For example, some people may feel that if they test positive, they will not have children. Persons who already have children may feel guilty because their children are at risk to have FSHD.

Career decisions

Will your test results affect your decisions about the type of work you are doing now or plan to do in the future? Do you plan to tell the people you work with about your decision to be tested or your test results?

Insurance issues

You should be comfortable with your insurance coverage (life, health and disability) prior to being tested. Potential problems can include: cancellation of existing benefits (unlikely), exclusions for coverage related to symptoms of FSHD, extended waiting periods for coverage, and an increase in costs for premiums. Some people may feel locked into a certain job to maintain insurance coverage. Life insurance may be especially difficult to obtain for persons with a positive test result.

COPING WITH RESULTS

You will most likely have strong emotional feelings when the results are given, regardless of the outcome. Many people feel relief at having an answer and disbelief that the answer is accurate. Often people express a feeling of “loss of identity”, particularly if the result is different from the one they expected. Frequently people go through a period of regretting past decisions that they might have made differently if they had known their status with regards to FSHD. This is particularly true if those decisions were permanent, for example, decisions about whether or not to have children, or

career paths. Most people eventually adjust well to their test results. It is important to draw on the support of professionals, family and friends. Some other feelings specific to the test result may be:

Positive test result in a person with no symptoms

Many people express a sense of isolation, feeling that there are few other people who can relate to their feelings. Participating in a support group or continued support from a genetics professional can help them feel they are not alone in dealing with the result. Some people will have difficulty with not knowing when they will first develop symptoms of facioscapulohumeral dystrophy. An appointment with a neurologist or neurogeneticist can help determine if a person is beginning to show signs of FSHD. Feelings such as depression, anger, loss of hope, despair and severe stress can occur. If these feelings occur, treatment by a psychologist, psychiatrist or counselor can be very helpful. The sense of "riding an emotional roller coaster" with good days and bad days is normal. Most people eventually come to terms with their results and use the information to help them make plans for the future.

Positive test result in a person with symptoms

For some people it is a relief to actually have an explanation for physical problems they may have been experiencing. Sometimes this information can reduce stress in the work environment because a person with FSHD may be eligible for job reclassification or medical benefits. As with the diagnosis of any chronic illness, the diagnosis of FSHD can bring feelings of shock, grief, anger, disbelief, depression, hopelessness and loss of control. Professional support and support from friends and family can be helpful during this difficult time. In addition, an evaluation by a physiatrist, a physician whose focus is on restoring function, can help a person with FSHD continue to lead a productive and satisfying life.

Uncertain results

This can be the most frustrating result since the at risk person chose to be tested in order to have an answer.

Negative or normal result

Most people feel joy and relief with a negative result but may experience a low period following the testing. They may be disappointed that the "good news" did not bring as many positive

changes in their life as anticipated. The problems that existed before the FSHD testing are most likely still there. Facioscapulohumeral dystrophy is still very much a part of their family life. Often there may be a feeling of increased responsibility for caring for affected family members. They may feel a new pressure to "make something of themselves". They may also feel guilty that they have not inherited FSHD when other close family members have, particularly if they are the only family member who has escaped the disease.

TESTING OF CHILDREN

Testing is not offered to children under the age of legal consent (age 18) except in cases where a child may be having signs of FSHD. There is no medical reason to test a child without symptoms of FSHD. When children become legal adults they may make their own choice about testing. Children who are suspected of having symptoms of FSHD should be evaluated by a pediatrician, a neurogeneticist or neurologist. In a child with symptoms, FSHD testing may be an important part of evaluating the child's medical problems.

PRENATAL TESTING

Genetic testing can be done during pregnancy to determine if an unborn baby (fetus) has inherited the deletion for FSHD. This testing may be done if a parent has tested positive. If a parent has tested positive and the fetus is found to have inherited a deletion for FSHD, the deletion size cannot be used to predict the severity of symptoms in the child with 100% accuracy. If a fetus tests positive for FSHD, the options are to terminate the pregnancy, or carry the pregnancy to term. This type of testing raises several difficult ethical questions. For some people, termination of pregnancy or abortion is not an option under any circumstances. Others feel that a child should not be brought into the world if he or she will develop FSHD. If the parents choose not to terminate an affected pregnancy, then genetic testing will have been done on a child. Whether or not to terminate a pregnancy for FSHD is a very difficult decision. In the situation where a parent has tested positive, ideally the risks of prenatal diagnosis techniques of amniocentesis and chorionic villi sampling (CVS) should be thoroughly discussed with a genetic counselor *prior* to pregnancy and before undertaking prenatal diagnosis.

Within the last several years, a new technique has become available that allows genetic testing of embryos prior to pregnancy. This technique is called preimplantation genetic diagnosis (PGD). Currently, PGD is not technically possible nor available for facioscapulohumeral dystrophy.

RESEARCH

Genetic testing for FSHD has only been available for a few years. As more people participate in testing for FSHD, our knowledge of the long-term psychological effects of this testing will improve so that we can better support people through this difficult process. As of yet, the mechanisms that cause FSHD are not understood. As our understanding is improved through research, hopefully the ability to treat and manage this condition will improve. There is a great deal of research being done on facioscapulohumeral dystrophy and related muscular dystrophies. Receiving information from the Muscular Dystrophy Association and the FSH Society is an excellent way to stay informed about new advances.

RESOURCES

Facioscapulohumeral (FSH) Society, Inc
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Muscular Dystrophy Association (MDA) – USA
National Headquarters
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Email: mda@mdausa.org
Web: http://www.mdausa.org/home.html

National Society of Genetic Counselors (NSGC)
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Web: http://www.nsgc.org

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