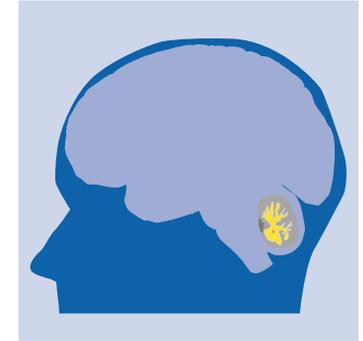


Spinocerebellar Ataxia: Making an Informed Choice About Genetic Testing



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This booklet provides information about dominant forms of spinocerebellar ataxia (SCA) and genetic testing for SCA. Spinocerebellar ataxia is an inherited disorder of brain function. It is characterized by increasing problems with coordination that often affect the legs, hands and speech. There are 11 types of SCA that have been described. These types are given numbers (1-12, excluding the number 9) and they share many similarities and symptoms. The numbers do not imply increasing severity. Rather, SCA 1 was the first type of spinocerebellar ataxia to be linked to a specific chromosome, SCA 2 was the second, and so on. At this time, genetic testing is available for several types of SCA (types 1, 2, 3, 6, and 7). The decision to be tested is a personal one, and each person must make his or her own informed choice about testing.

DEFINING ATAXIA

Ataxia is a symptom, not a specific disease or diagnosis. Ataxia means poor coordination of movement. The term ataxia is most often used to describe walking that is uncoordinated and unsteady. Ataxia can affect fingers, hands, arms, speech (dysarthria) and eye movements (nystagmus). There are many causes of ataxia.

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This booklet is available online through the Rehabilitation Research and Training Center in Neuromuscular diseases at UC Davis website:

<http://www.rehabinfo.net>

and the author's website:

<http://depts.washington.edu/neurogen>

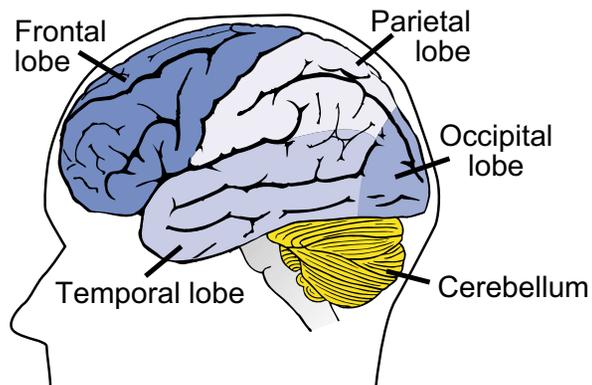


Figure 1. Diagram of the brain. The cerebellum is the part of the brain primarily affected in SCA.

In most cases, ataxia results from damage to or shrinkage (atrophy) of the cerebellum, the part of the brain that controls coordination of movement (See Figure 1). There are two main categories of ataxia, acquired and hereditary:

Acquired (non-genetic) ataxia

This type of ataxia usually results from some type of environmental factor such as a brain injury, tumor or chemical exposure. For example, head trauma or stroke can cause ataxia. Exposure to high levels of alcohol can lead to ataxia. A brain tumor can cause a person to become ataxic. Acquired ataxia is not passed on in families, so the children of an affected person are not at an increased risk to develop ataxia.

Hereditary ataxia

Hereditary ataxia is passed on in families, and shows a clear inheritance pattern. Most types of hereditary ataxia are inherited in an autosomal dominant pattern, some types in an autosomal recessive pattern (Friedreich ataxia) and rarely, in an X-linked pattern (refer to section on **Inheritance of SCA** and see Figures 2 and 4). In general, the hereditary ataxias are slowly progressive and are associated with atrophy of the cerebellum that can be seen on a brain scan.

Friedreich ataxia (FA) is one of the most common types of inherited ataxia. People with FA usually begin to show symptoms during their childhood or teenage years. In contrast to most types of SCA, many people with Friedreich ataxia lose the ability to walk by their mid-20s, and FA can often shorten lifespan because it often affects the heart. FA can usually be distinguished from SCA based on age of onset, clinical symptoms and genetic testing. In addition, FA is inherited in an autosomal recessive pattern, so only one generation of a family is affected. For these reasons, this booklet will only provide information about the dominant spinocerebellar ataxias and not FA. To learn more about Friedreich ataxia, contact the National Ataxia Foundation (refer to section on **Resources**).

DESCRIPTION OF SPINOCEREBELLAR ATAXIA

All types of spinocerebellar ataxia are characterized by a progressive incoordination of walking. In addition, they are often associated with poor coordination of hand movements, eye movements, and speech (See Table 1). With some exceptions, the onset of symptoms usually occurs **after** the age of 18 (“adult-onset”). Spinocerebellar ataxia is slowly progressive, which means that symptoms of the condition gradually worsen over a period of years. Some types of SCA can progress more rapidly than others. Brain scans such as magnetic resonance imaging (MRI) and computerized tomography (CT) of affected persons often show shrinkage or atrophy of the

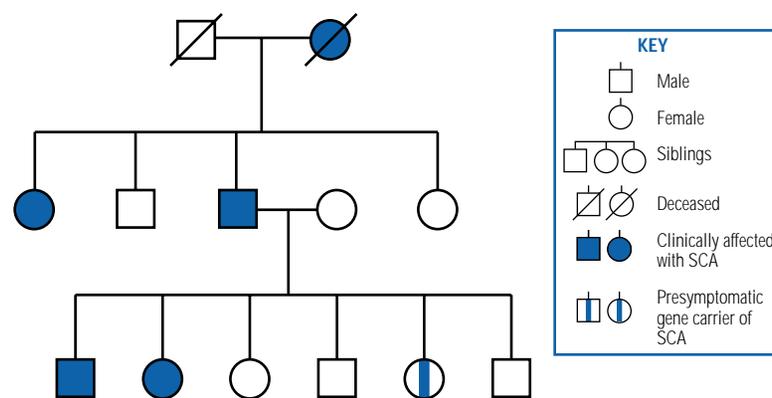


Figure 2. Family tree (pedigree) of a family with spinocerebellar ataxia showing autosomal dominant inheritance and a female who has tested positive for an SCA gene.

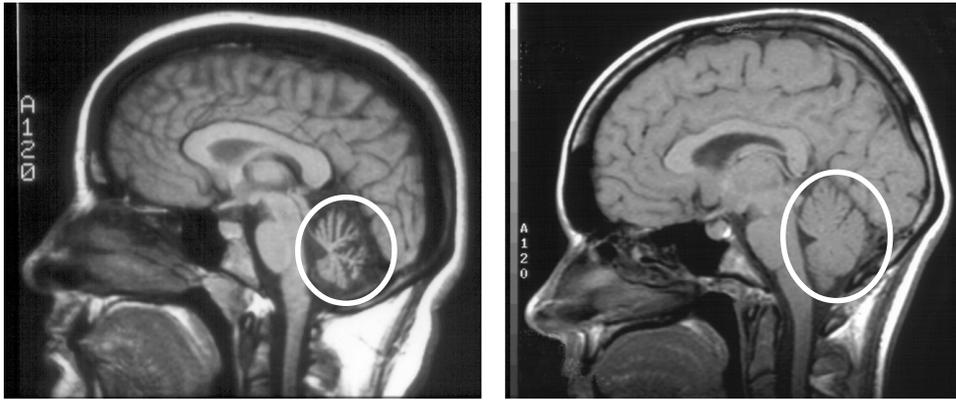


Figure 3. MRI scans of two brains. The brain on the left shows atrophy of the cerebellum in a person with SCA. The brain on the right shows a normal cerebellum.

cerebellum that becomes more noticeable as the disease progresses (see Figure 3 above). At this time, there is no cure or treatment that can prevent or slow the progression of symptoms or cerebellar atrophy.

Because there is an overlap of symptoms among the different types of spinocerebellar ataxia, genetic testing is needed to determine with certainty the type of SCA in an affected person. However, genetic testing cannot always provide a clear diagnosis. This is because SCA types 1, 2, 3, 6 and 7 account for only about 50-60% of all dominant hereditary ataxias. Consequently, if a person who clearly is affected with hereditary ataxia has a normal genetic test result, it could mean that he or she has a type of SCA for which there is no genetic testing. In this situation, genetic testing is not useful for relatives of the affected person. A neurological examination can be done on family members who are concerned they may have symptoms of ataxia. In the future, it is likely that genetic testing will become available for other types of SCA. The affected person can have genetic testing for other types of SCA as it becomes available. To ensure that future genetic testing can be done, you may want to discuss storage of genetic material (DNA banking) with a genetic counselor or medical geneticist.

Table 1. General description of the types of spinocerebellar ataxia. (The number 9 is not used)

Type	Frequency in dominant ataxias in North America	Average age of onset (years) (range)	Average duration of disease (years) (range)	Other distinguishing features (all types show ataxia)
SCA 1	6%	30s (<10 - >60)	15 (10-28)	Active reflexes
SCA 2	15%	20s - 30s (<10 - >60)	10 (1-30)	Slow eye movements, sometimes dementia
SCA 3	21%	30s (10 - 70)	10 (1-20)	Muscle weakness and atrophy. Originally called <i>Machado-Joseph disease</i> .
SCA 4	Rare	30s - 40s (19 - 59)	Decades	Sensory loss
SCA 5	Rare	20s - 30s (10 - 68)	>25	Early onset and slow worsening of symptoms
SCA 6	15%	40s - 50s (19 - 71)	>25	Very slow worsening of symptoms
SCA 7	5%	20s - 30s	20 (1-45)	Visual loss
SCA 8	2-5%	Late 30s (18-65)	Normal lifespan	Active reflexes and decreased sensation
SCA 10	Rare	Mid 30s	9	Occasional seizures
SCA 11	Rare	20s - 30s (15-55)	Normal lifespan	Very slow worsening of symptoms
SCA 12	Rare	Mid 30s (8-55)	Not known	Tremor, sometimes dementia

INHERITANCE OF SCA

All types of SCA are inherited in an autosomal dominant pattern. This means each son or daughter of an affected person has a 1 in 2, or 50% chance of inheriting SCA. Spinocerebellar ataxia affects males and females equally. Each type of SCA is caused by a change (mutation) in a specific gene that is needed for normal brain function. (see Table 2)

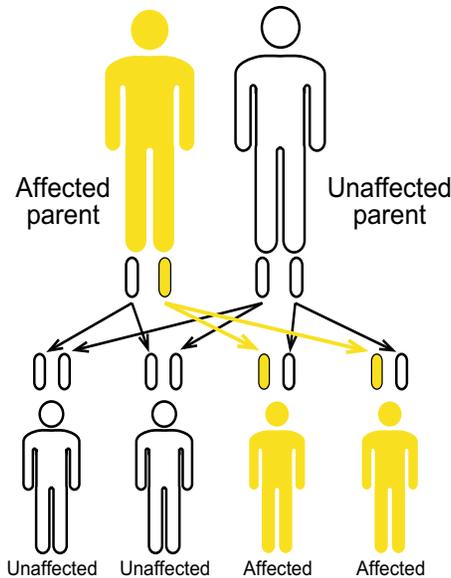


Figure 4. Diagram of autosomal dominant inheritance. Each child has a 50% chance of inheriting SCA from an affected parent.

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 50,000 to 100,000 genes. Genes, in turn, are packaged on chromosomes—threadlike structures within cells that can be seen with a microscope (genes cannot be seen under the microscope). Each person inherits half of their chromosomes from their father, and half from their mother. Every person has 23 pairs of chromosomes that contain two copies of each gene.

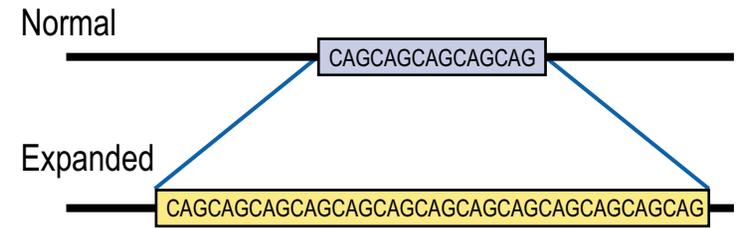


Figure 5. Diagram of CAG repeat expansion.

The genetic change that causes SCA types 1, 2, 3, 6, 7 and 12 is called a CAG repeat expansion (See Figure 5). CAG represents a specific pattern of DNA. In these types of spinocerebellar ataxia, the CAG pattern is repeated too many times, and disrupts the normal function of the protein made by the gene (See Table 2). The exception is SCA type 8, which is caused by a CTG repeat expansion. There is genetic testing for SCA types 1, 2, 3, 6 and 7, and it will be available soon for SCA type 8. The genes for SCA types 4, 5, 10 and 11 have not been discovered yet.

Anticipation and penetrance

Spinocerebellar ataxia types 1, 2, 3 and 7 are characterized by a phenomenon called anticipation. Anticipation refers to an earlier age of symptoms and increasing severity of disease from generation to generation in a family. In other words, an affected child can have more severe disease than their affected parent. With the recent

Table 2. Genetic Aspects of SCA.

Type	Chromosome location of gene	Normal repeat size	Expanded repeat size
SCA 1	6	6-36	39-83
SCA 2	12	15-31	34-220
SCA 3	14	12-40	55-86
SCA 6	19	4-18	21-33
SCA 7	3	4-19	37-300
SCA 8	13	16-34 (CTG)	About 100-250 (CTG)
SCA 12	5	7-28	66-78

discovery of the genetic cause of SCA types 1, 2, 3 and 7, the biologic basis of anticipation in these conditions is beginning to be explained. It has been found that the repeat size can change when passed from parent to child. For example, if a parent has a specific repeat size on genetic testing, a child may have a larger number of repeats. Anticipation cannot be predicted. In most types of spinocerebellar ataxia, there is a general association between repeat size, age of onset and severity of symptoms. In general, the larger the repeat size, the younger the age at which a person will develop symptoms of SCA. On the other hand, the repeat size cannot be used to predict the exact age when a person will develop symptoms, or exactly what those symptoms will be like.

The term penetrance refers to the proportion of individuals with the gene for SCA who will actually develop symptoms. In all types of SCA, penetrance is very high, meaning that almost everyone with a repeat expansion will develop symptoms of SCA at some point in their lifetime. In some cases, however, a person with a repeat expansion may die of other causes before showing symptoms of SCA. For reasons that are not completely understood, a few people with a repeat expansion may never develop symptoms of SCA (“non-penetrance”). Further research is needed to understand why non-penetrance occurs in SCA.

DNA TESTING

Genetic testing can be done to find out whether or not a person has inherited the CAG repeat expansion for SCA types 1, 2, 3, 6 and 7. The testing can be done on a blood sample or tissue sample. Usually if the type of SCA has not been determined in a family or affected person, testing is done for SCA types 1, 2, 3, 6 and 7. If the type of SCA in the family is known, then only that type of SCA will be tested for. Testing for SCA usually takes between 2-4 weeks for results.

There are three possible outcomes from DNA testing:

Negative/Normal

If a parent or other affected relative is already known to have a repeat expansion for a specific type of SCA, this result means that the person being tested has not inherited the repeat expansion for that type of SCA. The CAG repeat number will fall into the normal range specific to that type of SCA. The accuracy of this result is

close to 100%. A person can be affected with SCA and still have a negative test result. This can happen if the person has a type of SCA for which testing is not available.

Positive

This result means that a person has inherited a repeat expansion for a specific type of SCA. The repeat number falls into the expanded range for that type of SCA. The accuracy of this result is close to 100%. A positive result does not mean that a person has any physical signs of SCA, nor does it tell at what age a person will begin to show signs of SCA, or exactly what those symptoms will be like. A positive result usually means that at some point in that person's lifetime, he or she will develop signs of SCA. However, there is variability in the symptoms, the severity of symptoms, the rate of symptom progression, as well as the age of disease onset even within the same family. In rare cases, a person with a positive result may never develop symptoms of SCA for reasons that are not understood (non-penetrance). Persons with symptoms of SCA should be seen by a neurologist who can confirm the diagnosis and provide continuing medical care and support.

Uncertain

There is an area of uncertainty or “gray area” in SCA genetic testing. If the repeat size falls inbetween the normal and the expanded range, that person may or may not develop symptoms of SCA. Less than 2% of persons who are tested fall into this range. Children of this person may be at risk to inherit a repeat expansion that increases in size when passed from parent to child (anticipation). As a result, the child may inherit a repeat expansion that is now clearly within the range seen in affected persons.

TESTING PROCESS

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

Symptomatic and presymptomatic testing

There is a big difference between genetic testing done to find the cause of ataxia in an affected person (symptomatic testing) versus genetic testing for a person who is at risk for SCA and has no symptoms of the condition (presymptomatic testing). For a person

with symptoms, testing for SCA 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 SCA. 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 individuals considering presymptomatic testing for SCA, but may also be useful for those with symptoms of SCA who are undergoing testing.

Confirmation of SCA in the family

It is very important to confirm the diagnosis and type of SCA in the family. Often medical records on affected family members are requested. It is most useful to perform the DNA blood test on an affected family member to confirm the presence of a repeat expansion for SCA typing.

Genetic counseling

Genetic counseling is an essential part of the presymptomatic testing process. Genetic counseling involves education and counseling 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 SCA. Persons with symptoms may discuss testing with a neurologist.

Support person

The decision of whether or not to have testing for SCA 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 visits 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 exam) is under \$1,200. Some insurance companies will cover the costs 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 SCA, the main benefit of presymptomatic testing is psychological, since there is currently no medical intervention (for example, early treatment, specific diet, or lifestyle changes) that can slow or prevent spinocerebellar ataxia. The test results have important implications for many life decisions. Here are just some of the issues to think about:

Timing of testing

The process of being tested for SCA and dealing with the results will be stressful and is often 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, while in the middle of a divorce or break-up of a relationship, or at 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, right before or after marriage, or during important holidays.

It is easy to become consumed with thinking about testing for SCA. 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 SCA 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, do some planning about who 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? People who are at risk for SCA may fear abandonment by their spouse or significant other when they develop signs of the condition. Have you discussed this fear or other fears with your partner?

Child - Do your children know about SCA? 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 SCA gene, 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 SCA gene you may experience “survivor guilt,” meaning that you wonder why you have escaped this disease whereas others in your family have not. 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 SCA and your decision about 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 feel that if they test positive, they will not have children. Individuals who already have children may feel guilty about having had children because they may develop SCA.

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 SCA, 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.

Do you think you have inherited spinocerebellar ataxia ?

Honestly considering your feelings about whether or not you believe you have or will develop SCA is important. It can be more difficult to deal with the test results if they are the opposite of your inner feelings.

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. Often people go through a period of regretting past decisions, which they might have made differently if they had known their status with regards to SCA. 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. Try to draw on the support of professionals, family and friends.

Some other feelings specific to each test result may be:

Positive or high risk 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 an ataxia 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 a hard time with not knowing when they will first develop symptoms of spinocerebellar ataxia. They, their friends and relatives, may wonder if the occasional clumsiness or loss of balance is the beginning of SCA. A visit with a neurologist or neurogeneticist can help determine if a person is starting to show signs of SCA. 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 them to help make plans for the future.

Positive test result in a person with symptoms

For some people it is a relief to have an explanation for some of the problems they may have been having. Sometimes this information can reduce stress in the work environment. The person with SCA may be eligible for job reclassification or benefits. Stress in the family may also be reduced. As with the diagnosis of any chronic illness, the diagnosis of SCA can bring feelings of shock, grief, anger, disbelief, depression, hopelessness and loss of control. Professional support, and support from friends and family, can help someone with SCA continue to lead a productive and satisfying life.

Uncertain results

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

Negative or normal result

Most people feel joy and relief with a negative result but may experience a low period after 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 SCA testing are most likely still there. Spinocerebellar ataxia is still very much a part of their life. Often there may be a feeling of increased

responsibility for caring for affected family members. People who have lived their lives feeling they would not live a long life because they would some day develop SCA may have a hard time dealing with the concept of “having a future.” They may feel a new pressure to “make something of themselves.” They may also feel guilty that they will not develop SCA when other close family members will, 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 rare cases where a child may be having signs of SCA. There is no medical reason to test a child without symptoms of SCA. When children become adults they may make their own choice about testing. Children who are suspected of having symptoms of SCA should be examined by a neurologist.

PRENATAL TESTING

Genetic testing can be done during pregnancy to find out if an unborn baby (fetus) has inherited a gene for SCA if a parent has tested positive. This type of testing raises difficult ethical questions. If a fetus is found to have inherited SCA, the options are to terminate the pregnancy, or carry the pregnancy to term knowing the child will someday develop SCA. 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 someday suffer from SCA. If the parents choose not to terminate an affected pregnancy, then genetic testing will have been done on a child. For this reason, prenatal testing for SCA is strongly discouraged unless the parents plan to end an affected pregnancy. Also, with few exceptions, SCA is an adult onset condition, and most people enjoy a meaningful and productive life both before and after the onset of the condition. Whether or not to terminate a pregnancy for SCA is a very difficult decision; ideally this issue, as well as the risks of the prenatal diagnosis techniques of amniocentesis and chorionic villi sampling (CVS), should be thoroughly discussed *prior* to pregnancy and before undertaking prenatal testing.

RESEARCH

Direct tests for SCA types 1, 2, 3, 6 and 7 have only been available for a few years. Tests for more types of SCA will likely become available in the near future. As more people are tested for SCA, our knowledge of the long-term psychological effects of this testing will increase. This will allow us to better support people through this difficult process. As of yet, the mechanisms that cause SCA are not understood. As our understanding is increased through research, hopefully the ability to treat and manage this condition will improve. There is a great deal of research being done on the spinocerebellar ataxias and related neurological conditions. Receiving the National Ataxia Foundation newsletter is an excellent way to stay informed about new advances.

RESOURCES

National Ataxia Foundation (NAF)
2600 Fernbrook Lane, Suite 119
Minneapolis, MN 55447
Phone: (612) 553-0020
Fax: (612) 553-0167
Email: naf@mr.net
Web: <http://www.ataxia.org>

National Society of Genetic Counselors (NSGC)
233 Canterbury Drive
Wallingford, PA 19086-6617
Phone: (610) 872-7608
Fax: (610) 872-1192
Email: nsgc@aol.com
Web: <http://www.nsgc.org>

International Network of Ataxia Friends (INTERNAF)
Web: <http://internaf.merseyside.org>

REFERENCES / FURTHER READING

GeneClinics (online medical genetics knowledge base)
Ataxia Overview and *Spinocerebellar Ataxia Profiles*
<http://www.geneclinics.org>

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