Although genetic tests for known spinocerebellar ataxia (SCA) genes are increasingly available, their exact clinical role has received much less attention. Currently available DNA tests can define the genotypes of up to two thirds of patients with dominantly inherited SCAs. Certain characteristic clinical features and ethnic predilection of some of the SCA subtypes may help prioritize specific SCA gene testing. Available data on genotype-phenotype correlation suggest that currently available DNA tests cannot accurately predict age of onset or prognosis. Because of the mostly adult-onset symptoms and the absence of effective treatment, genetic counseling is essential for addressing ethical, social, legal, and psychological issues associated with SCA DNA testing.

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GENETIC CLASSIFICATION

Spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases characterized by cerebellar dysfunction alone or in combination with other neurological abnormalities. Spinocerebellar ataxias have become a focus of human genetics research since expansions of coded CAG trinucleotide repeats were shown to cause several dominantly inherited SCAs (SCAs 1, 2, 3, 6, and 7) and dentatorubral pallidolysian atrophy (DRPLA).1-3 Another dominant ataxia with an expanded CAG repeat in the TATA box binding protein (TBP) gene has been added recently to this group of disorders.4 In these disorders, the CAG triple repeat expansion gives rise to an elongated polyglutamine tract in the respective proteins, leading to a gain in function that is toxic to neurons. However, untranslated repeat expansions also cause dominantly inherited ataxic disorders. Spinocerebellar ataxia type 12 shows an expanded CAG repeat in the 5’ untranslated region of PPP2R2B, a gene coding for a brain-specific regulatory subunit of the protein phosphatase PP2A.5 Spinocerebellar ataxia type 8 is associated with an expansion of a CTG repeat in the 3’ untranslated region of the SCA8 gene that produces antisense messenger RNA to the KLHL1 gene on the complementary strand.6 In SCA10, the disease-causing expansion occurs in the ATTCT pentanucleotide repeat of intron 9 of SCA10, a gene of unknown function widely expressed in the brain.7 Five additional SCA loci have been mapped: SCA4 to 16q24-qter,8 SCA5 to 11q13, SCA6 to 15q1-21.3,9 SCA13 to 19q13.3-q13.4,10 and SCA14 to 19q13.4-qter.11 Episodic ataxia types 1 and 2 are also dominantly inherited cerebellar ataxias; they are caused by point mutations within a voltage-gated potassium channel gene (KCNA1) and the cerebral P/Q-type calcium channel α1 subunit gene (CACNL1A4), respectively.12,13 The most common recessively inherited ataxia is Friedreich ataxia (FRDA), which is caused by an expansion of the GAA repeat in intron 1 of the FRDA gene.14 Other recessive ataxias include vitamin E deficiency (due to α-tocopherol transfer protein deficiency or abetalipoproteinemia), ataxia telangiectasia, infantile-onset spinocerebellar ataxia (IOSCA), Marinesco-Sjogren syndrome, spastic ataxia of Charlevoix-Saguenay, Refsum disease, carbohydrate-deficiency ataxia, and Cayman Island ataxia, among others15 (also see the Washington University ataxia classification16). Wilson disease may mimic...
features of SCAs. Genetic testing is a powerful way of confirming the diagnosis and distinguishing various SCA subtypes, although there have been previous attempts to classify them according to their clinical presentations.17

**TYPES OF GENETIC TESTS**

Although genetic testing for known SCA genes is increasingly available, their exact clinical role has received much less attention. Currently available commercial DNA tests can define the genotypes of up to two thirds of patients with dominantly inherited SCAs10 (Table; see also Web site www.genetests.org,18 which catalogs genetic testing). As the list of these DNA tests grows, the variable and overlapping phenotypic manifestations of the SCA subtypes make it difficult to choose which specific SCA DNA test to order initially. Although a positive DNA test result provides the unequivocal diagnosis and distinguishes various SCA subtypes, although there have been previous attempts to classify them according to their clinical presentations.17

**CHOICE OF GENETIC TEST**

In general, these tests should be done in SCAs that demonstrate a clear mode of inheritance (Figure). For those without family history, secondary causes, especially treatable ones, should be excluded first. However, testing in apparent “sporadic” cases might be worthwhile if the family history is unreliable or ambiguous because about 5% of sporadic cases have been found to be autosomal dominant.20 A positive family history may not always be available for patients with SCA6 and recessive ataxias such as FRDA. A de novo mutation, ie, an expansion of an in-frame repeat, may become available for patients with SCA6 and recessive ataxias such as FRDA. A de novo mutation, ie, an expansion of an in-frame repeat, may become available for SCAs 10 and 12 and the ataxia with the TBP CAG expansion in the near future. DNA testing for point mutations may also be available on a research basis for ataxia telangiectasia, ataxia of vitamin E deficiency, mitochondrial disorders, Wilson disease, Refsum disease, and episodic ataxia types 1 and 2. However, screening of point mutations in these diseases are generally not cost-effective because each family can carry a different mutation, and their diagnoses should be based on clinical and other laboratory findings at present (Figure). New technologies, such as DNA microchip arrays, may make DNA testing for these diseases commercially feasible in the near future.
was originally described in 1972 in 2 families of Azorean descent. However, the CAG repeat expansion that causes MJD/SCA3, has been found in different ethnic populations with SCA3 around the world. Spino cerebellar ataxia type 3 seems to be most common in countries such as the United States, China, and Germany; SCAs 1 and 2 in the United Kingdom and Italy; SCA2 in India and Cuba; and SCAs 3 and 6 in Japan. Spino cerebellar ataxia type 10 has been seen only in Mexicans.7 Dentatorubral pallidoluysian atrophy is rare outside Japan. Spino cerebellar ataxia types 5, 6, and 14 have been reported in northeast Asia. Presence of a founder effect could possibly create different prevalences within the same ethnic population. For instance, this might in part explain why SCA1 is more common in northern Italy and SCA2 in the United States, China, and Germany; SCAs 1 and 2 in the United Kingdom and Italy; SCA2 in India and Cuba; and SCAs 3 and 6 in Japan. Spino cerebellar ataxia type 10 has been seen only in Mexicans.7 Dentatorubral pallidoluysian atrophy is rare outside Japan. Spino cerebellar ataxia types 5, 6, and 14 have been reported in northeast Asia. Presence of a founder effect could possibly create different prevalences within the same ethnic population. For instance, this might in part explain why SCA1 is more common in northern Italy and SCA2 is more frequent in southern parts of the country.

In addition to the wide phenotypic overlap among the SCAs, significant interfamilial and intrafamilial phenotypic variability exists even for each SCA subtype. However, it is worthwhile noting characteristic features of some SCAs.3,5 Markedly reduced velocity of saccadic eye movements, areflexia, and changes similar to those seen in olivopontocerebellar atrophy on magnetic resonance images of the brain suggest SCA2. Spino cerebellar ataxia type 7 is characterized by macular degeneration. Combinations of protruded eyes, muscle fasciculations, spasticity, chorea, gaze-evoked nystagmus, parkinsonism, and peripheral neuropathy favor MJD/SCA3, but SCA1 and SCA12 also share some of these features. Spino cerebellar ataxia types 5, 6, 10, and 11 should be considered in patients with relatively pure cerebellar signs. Patients with SCA13 characteristically show slowly progressive cerebellar ataxia of early childhood onset, with mild mental retardation and motor developmental delay. There are some overlapping clinical features between SCA6 and episodic ataxia type 2 and familial hemiplegic migraine.2,3,4 It is not surprising because the CAG expansion in SCA6 is located in the alpha-1A voltage-dependent calcium channel gene, and episodic ataxia type 2 is caused by a point mutation in the same gene. If there is a history of seizures with ataxia, DRPLA and SCA10 need to be considered; in the latter, seizures are accompanied by relatively pure cerebellar ataxia. Spino cerebellar ataxia type 3 and DRPLA need to be considered in patients with suspected Huntington disease (HD) whose HD DNA test results were normal because of some shared features. Some patients with SCA3 may show a pure parkinsonian phenotype. Most families with SCAs that are caused by polyglutamine-coding CAG expansions show

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### Genetic Testing for Ataxias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Repeat (Cryptic Sequence)</th>
<th>Normal Range</th>
<th>Intermediate Range</th>
<th>Disease Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRDA</td>
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<td>6-44</td>
<td>. . . †</td>
<td>40-82</td>
</tr>
<tr>
<td></td>
<td>CAG (CAA)</td>
<td>14-31</td>
<td>34-35</td>
<td>34-59</td>
</tr>
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<td>55-200</td>
</tr>
<tr>
<td></td>
<td>CAG (none)</td>
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<td>. . .</td>
<td>21-33</td>
</tr>
<tr>
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<td>28-35</td>
<td>37-.&gt;300</td>
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<td></td>
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<td>100-250‡</td>
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<tr>
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<td>10-22</td>
<td>. . .</td>
<td>&gt;1000</td>
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<tr>
<td></td>
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<td>. . .</td>
<td>49-88</td>
</tr>
<tr>
<td></td>
<td>GAA (none)</td>
<td>7-28</td>
<td>. . .</td>
<td>120-.&gt;1700</td>
</tr>
</tbody>
</table>

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Clinical algorithm for genetic testing for spino cerebellar ataxia (SCA). If the family history suggests an autosomal recessive or uncertain inheritance pattern, consider recessive diseases that can be tested. If test results for these diseases are negative, consider other recessive diseases by clinical phenotype and, if feasible, examine linkage for known recessive ataxia loci, which may lead to a specific diagnosis. Then, the patient can undergo DNA testing for the dominant ataxias after assessing the possibility of dominant inheritance with incomplete family history, reduced penetrance, and de novo mutation. If there is no family history it is important to exclude various secondary causes because specific treatment may be available. When these are excluded, consider the recessive diseases, such as Friedreich ataxia (FDRA), and then the certain autosomal dominant SCAs if the clinical suspicion is strong. Prioritize the tests for dominant ataxias based on the ethnic origin and the clinical phenotype. At present, there are no direct DNA tests for detection of the mutations for SCAs 4, 5, 11, 13, and 14. AVED indicates ataxia of vitamin E deficiency; AT, ataxia telangiectasia; and DRPLA, dentatorubral pallidoluysian atrophy.
anticipation, ie, earlier disease onset with increasingly severe disease phenotype in succeeding generations.\textsuperscript{1,2} Spinocerebellar ataxia types 5, 10, and probably 14 also show anticipation,\textsuperscript{7,9,12} whereas SCAs 8, 12, and 13 do not.\textsuperscript{4,5,10} Our experience suggests that the predictive value of some of these characteristic clinical features may increase when applied to a particular ethnic population in which the most common SCA subtypes are known. Further studies may make it possible to compute the probabilities of SCA subtypes based on these factors for each patient.

LIMITATIONS

Cautious interpretation of an SCA test result and understanding of its implication are vital in genetic counseling and patient care. Anticipation observed in most SCAs accompanies progressive increases of expanded CAG repeats in successive generations, often depending on paternal transmission. Patients with larger CAG repeats generally show earlier ages of onset, with greater disease severity than those with relatively smaller repeats. A similar mechanism involving the ATTCT repeat seems to explain anticipation in SCA10 families. However, because the repeat size accounts for only up to 60% of the variability of age of onset, we cannot predict the exact age of onset for a given size of a disease allele of any SCA subtype.\textsuperscript{1,3} Although individuals undergoing predictive testing frequently ask for prediction of age of onset and prognosis, further research regarding other genetic and environmental determinants are required before we can answer this question. There seems to be a critical size of repeat for most of the SCAs above which the disease would manifest. However, this is not absolute in some SCAs in which disease and normal allele sizes overlap in an intermediate range. Alleles in the intermediate range show reduced penetrance in SCA2. In SCA7, the intermediate alleles do not cause disease but can give rise to de novo expansion to the disease-causing allele in subsequent generations (Table). Further studies are needed in SCA8 to address the observation that fully expanded alleles show reduced penetrance in affected families and are also found in controls and other patients without SCA.\textsuperscript{3,6} Defining the risk of developing the disease in such instances is a difficult task. Effects of parental origin on repeat size instability may become an important subject in genetic counseling because paternal transmission of many SCAs (eg, SCAs 1, 2, and 3) may result in a severe, rapidly progressive phenotype at a young age. In SCA7, this phenomenon may be the most prominent in which increased embryonic lethality in paternal transmission has been postulated.\textsuperscript{21}

NONMEDICAL ISSUES

Despite the great advances in molecular genetics of SCAs, the phenotypic and genetic variability, the mostly adult-onset symptoms, and the absence of effective treatment make formulation of specific guidelines in genetic counseling of SCA a daunting task. Although at present there are no proposed guidelines for SCA testing, we must address the numerous ethical, social, legal, and psychological issues similar to those raised previously for HD (another trinucleotide repeat disorder with no effective treatment), including confirmatory testing, prenatal diagnosis, predictive testing and asymptomatic testing for children, confidentiality, insurability, finances, employment, disability, and marriage.\textsuperscript{22} With increasing availability of DNA testing for a growing number of SCAs, physicians will be confronted with many of these problems. Geneticists and experienced genetic counselors should shoulder this burden. However, physicians at tertiary and primary levels should also participate and, in some cases, may need to play a major role in this task. Testing in at-risk asymptomatic children has been generally discouraged. Prenatal testing of SCAs has been available, but few parents seem to be electing it. Issues such as termination of pregnancy in the event of a detectable mutation in the fetus and follow-up care for psychological problems require careful management by a team of physicians, genetic counselors, psychologists, and social workers. Great effort should be accorded to predictive testing, which usually creates the most distress in those tested. A study conducted by Nance and colleagues\textsuperscript{23} before the discovery of the SCA1 gene revealed that about two thirds of 117 patients, spouses, and at-risk individuals of 2 SCA1 kindreds wanted predictive testing immediately and 42% thought prenatal testing should be made available. Members of one kindred demonstrated a significantly higher level of anticipated adverse psychological responses such as depression, anger, and suicidal thoughts. Cooperative efforts to establish guidelines for this issue are needed. Experiences in HD are invaluable in this process; however, keep in mind that there are important differences between each SCA subtype and HD, especially in their psychological and social needs.

FUTURE CHALLENGES

Increasing understanding of the pathogenic mechanisms in SCAs caused by polyglutamine expansions and FRDA may lead to exploitation of new effective therapeutic drugs in the near future.\textsuperscript{24,25} Today, experimental neuroprotective drugs (such as N-methyl-D-aspartate antagonists) are already available for trials.\textsuperscript{26} Developing a reliable ataxia rating scale to monitor disease progression and treatment response has been initiated.\textsuperscript{27} The future availability of therapeutic interventions would drastically change the indications of DNA testing and its psychological and social impacts. Analyses of cost-effectiveness of DNA testing and its potential social implications are also important. Cloning of genes of SCAs 4, 5, 11, 13, and 14 and other unclassified hereditary SCAs, further understanding of genotypic-phenotypic correlations, and studies of susceptibility loci and disease-modifying genes would be translated into more comprehensive genetic testing programs.

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