State of the Art Review

Molecular Diagnosis of Inherited Movement Disorders
Movement Disorders Society Task Force on Molecular Diagnosis

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Abstract: This review is designed to provide practical help for the clinical neurologist to make appropriate use of the possibilities of molecular diagnosis of inherited movement disorders. Huntington's disease, Parkinson's disease and parkinsonian syndromes, ataxias, Wilson disease, essential tremor, dystonias, and other genetic diseases associated with a variety of movement disorders are considered separately. © 2002 Movement Disorder Society

Key words: Huntington's disease; Parkinson's disease; parkinsonism; autosomal recessive ataxias; autosomal dominant cerebellar ataxias; Wilson disease; essential tremor; primary torsion dystonia; genetic testing

OVERVIEW

Recent progress in molecular genetics has greatly expanded our knowledge of the molecular basis of many inherited neurological diseases. The chromosomal position of a large number of genes that, when mutated, can cause neurological dysfunction, is now known. In many cases, the genes themselves and their disease-causing mutations have been identified. This increasing wealth of knowledge has allowed the reclassification of a number of formerly heterogeneous clinical syndromes and provides novel diagnostic possibilities. It allows the characterization of pathologic gene products, thus providing further insight into the molecular pathogenesis of these disorders. Eventually, new approaches towards therapy and prevention will emerge. Today and in the years to come, keeping apace of the rapid advances in neurogenetics will be a challenge to neurologists everywhere.

Molecular genetic techniques have been particularly valuable in defining and classifying heterogeneous inherited movement disorder syndromes, such as the dystonias, and the spinocerebellar ataxias.

In clinical practice, the availability and limitation of molecular diagnosis depends on our present knowledge of the molecular genetic basis of the respective disease or group of diseases, but also on the degree of genetic complexity of the disorders under investigation. Some diseases, such as Huntington's disease, are caused by a specific mutation in a single gene,[1] and routine molecular diagnosis can be provided by a simple PCR-based assay. In other cases, however, for example in dopa-responsive dystonia, many different mutations can be found (allelic heterogeneity). Depending on the size of the gene, this

may render molecular diagnosis very costly and time-consuming and some mutations, like those situated in the introns affecting RNA-splicing or in regulatory sequences upstream of the coding region, may be difficult to detect on routine sequencing.

Despite the fact that only a small percentage of inherited movement disorders can be treated efficiently, molecular diagnosis is increasingly important, because it may provide valuable information for the affected individuals and their families in order to make informed choices on life and family planning. If genetic testing is able to identify the cause for neurological symptoms, subsequent exhaustive costly investigations will be avoided.

This review is designed to provide practical help for the clinical neurologist to make appropriate use of the possibilities of molecular diagnosis of inherited movement disorders. It should be emphasized that molecular testing may be a procedure of far-reaching consequences, both for the individual affected and for the entire family. It should, therefore, be performed only after careful consideration, including a genetic counseling process, in accordance with local regulations, which may differ considerably in different parts of the world. It may also be important to contact your area's Department of Health before ordering a diagnostic genetic test to confirm that the laboratory is approved to perform the test.

General Principles of Molecular Diagnosis

The primary goal of molecular diagnosis is to provide help for the individual patient, client and/or their families. Reducing the prevalence of inherited disorders in a population or in subsequent generations may be a secondary effect, but must never be allowed to guide the process of genetic counseling and diagnosis.

Genetic Counseling.

It must always be kept in mind that the molecular genetic diagnosis of an inherited disorder affects not only the patient, but also the entire family. Therefore, genetic counseling is an essential component of the diagnosis of inherited disorders. Sensitive and informed counseling provides patients and families with a foundation for decisions about testing. Patients should be counseled concerning the clinical features and course of their disease as well as over potential consequences for the family, taking into consideration the most important genetic parameters such as mode of inheritance and penetrance. Even if the test is negative, a genetic etiology is not excluded. If the test is positive, a diagnosis is secured but this diagnosis impacts on other at-risk family members. These members, even if asymptomatic, may wish carrier

testing, and genetic counseling for all asymptomatic family members needs to be done first. If the treating neurologist does not have thorough experience with inherited disorders, referral to an experienced counselor from a department of human genetics or another genetic counseling unit is strongly advised. In most situations, genetic testing should not be performed until adequate counseling has been provided.

Ethical dilemmas may arise from molecular testing, concerning matters of employment, insurance, and general life planning, that must be dealt with carefully on an individual basis.[2]

In the case of predictive testing, psychological counseling by appropriately trained persons is essential before testing and again after results have been disclosed.

Informed Consent.

As is true for all diagnostic procedures, the essential prerequisite for molecular diagnosis is the informed and voluntary consent of the patient. Therefore, the neurologist should establish that the patient or a lawful surrogate is capable of comprehending relevant information and is exercising informed choices. Molecular genetic diagnostic tests should not be performed at the request of members of the patients' families or other third parties (e.g., insurers, employers) without the express written consent of the patient.

Confidentiality.

Test results suggesting that patients or family members carry mutations that indicate or predict a major neurological disorder or a susceptibility to a neurological disorder are highly sensitive. Therefore, rigorous measures to ensure confidentiality should be taken. Test results should never be disclosed to a third party without explicit written consent from the patient or their lawful surrogates.

Presymptomatic Diagnosis.

The identification of disease genes allows presymptomatic (predictive) diagnosis in many cases. There may be risks associated with presymptomatic testing and these include an adverse emotional response, restricted access to insurance, discrimination in employment, and concerns about confidentiality. The decision for predictive testing should be undertaken only after appropriate counseling to permit an informed decision concerning the risks and benefits for the individual. Guidelines for presymptomatic diagnosis have been issued by the International Huntington's Disease Society and the World Federation of Neurology (WFN) research group for Huntington's disease.[3,4] These guidelines, which include ex-

tensive pre- and post-test counseling and thorough psychological support during the extensive process, should be followed in all cases of presymptomatic diagnosis. Generally, presymptomatic testing should be provided within the setting of a department of Human Genetics only. The same is true for prenatal diagnosis. If no clear therapeutic consequences can be envisioned, presymptomatic diagnosis should not be performed in minors.

Principles of Molecular Diagnosis

"Direct" Molecular Diagnosis, Mutational Analysis.

If the gene causing a neurological disorder is known, direct molecular diagnosis can be performed by mutational analysis. Only DNA from the affected individual is required. Usually, DNA is extracted from peripheral blood leukocytes, and exonic sequences, which are known to harbor mutations in the particular disorder under investigation, will be amplified by use of the polymerase chain reaction (PCR). Depending on the type of the mutation, it will then be detected either directly by gel electrophoresis (e.g., in the case of trinucleotide repeat expansions), gel electrophoresis following digestion by a suitable restriction enzyme (if a particular mutation alters a cutting site (restriction site) of a particular enzyme), or direct sequencing. If a gene is very large (genes with 30 and more exons are not uncommon) and mutations are scattered throughout the entire gene, direct mutational analysis can be very costly and time-consuming. In these cases, routine sequence analysis is sometimes offered only for portions of a gene, where mutations may be clustered.

"Indirect" Molecular Diagnosis.

Knowledge of the chromosomal position of a disease gene allows molecular support for the diagnosis, even if the disease gene itself is unknown or if analysis is unfeasible. "Indirect" molecular diagnosis is limited to risk determination for an individual in whose family an inherited neurological disease has already been diagnosed clinically or molecularly. The method is based on the analysis of DNA polymorphisms ("markers") known to be in close neighborhood (closely linked) to the disease gene under investigation. Determination of the marker alleles in healthy and affected family members allows the identification of the disease gene–bearing chromosome in this particular family. It must be emphasized that accurate clinical diagnosis in at least one affected family member is an absolute prerequisite for this type of molecular diagnosis and there is a small but definite error rate with this sort of linkage analysis. Until the gene for Huntington's disease was identified in 1993,

predictive testing for HD was the most widely used application for indirect molecular diagnosis. As more and more disease genes are identified, direct mutational analysis has become increasingly important.

Practical Approach to Molecular Diagnosis.

The patient confirms his informed consent to the procedure in writing. Usually, 10 to 20 ml of whole blood (EDTA or ACD for lymphocyte lines) are sufficient. The blood can be sent by mail to the laboratory without freezing or refrigeration. A delay of 3 to 5 days before DNA extraction is acceptable. It is obviously crucial that the tubes are clearly labeled, and that the clinical information including family history and the informed consent are contained within the shipment.

INHERITED MOVEMENT DISORDERS

HUNTINGTON'S DISEASE

Richard H. Myers and Judith A. Sinsheimer

Huntington's disease (HD), a dominantly transmitted neurodegenerative disorder involving the basal ganglia and cerebral cortex, typically strikes in mid-life but onset can occur at any age. The characteristic symptoms of HD are involuntary choreiform movements, cognitive impairment, mood disorders, and behavioral changes. The nature of the genetic defect, an unstable expanded CAG repeat within the coding region of a novel gene, explains many of the genetic features of the disorder, including the variability in age at onset, tendency of juvenile disease to be inherited from fathers, and sporadic appearance of new mutations to HD.[1]

A single diagnostic procedure can be performed to confirm or rule out the presence of a mutation associated with HD. Normal chromosomes possess from 6–26 CAG repeats that are inherited in a Mendelian fashion. HD chromosomes have from 40 to over 100 CAG-units. Exceptionally, alleles with 36–39 repeats can be found in unaffected elderly relatives of sporadic de novo cases of the disease. The identification of this genetic defect in HD makes it possible to offer a direct DNA test through polymerase chain reaction (PCR) amplification of *HD* CAG repeat. The length of the expanded CAG repeat is strongly inversely correlated with the age at onset of the disease. Nevertheless, any given expanded CAG repeat may be associated with a broad range of onset ages, indicating that the relationship of repeat size to onset age is not sufficiently strong to be used clinically to predict onset for subjects who are not yet symptomatic.

Currently four CAG repeat size ranges are recognized to be associated with varying disease risk in HD. These

ranges have been defined by the "US HD Genetic Testing Group" (USHDGTG) and are derived from information derived from more than 1,000 HD tests and from published sources. Nevertheless, the disease-related risk pertaining to the repeats in the 27 to 39 range has often been estimated from fewer than 10 observations at each repeat size and thus these risk estimates can be expected to change with additional experience.

Normal: Repeat Sizes Up to 26 Units

Persons with repeats in this range neither develop HD nor has there been a confirmed instance of a child inheriting HD from a parent with a repeat in this range.

Non-Penetrant with Paternal Meiotic Instability: Repeats of 27 to 35 Units

Repeats in this range are rare and represent approximately 1% of expanded alleles seen in HD testing programs. There have been no confirmed reports of persons with repeats in this range expressing HD. There are, however, confirmed cases of paternally transmitted meiotic instability such that descendants of fathers with repeats in this range are known to have inherited an expanded allele in the clinical range.

Reduced Penetrance with Meiotic Instability: Repeats of 36 to 39 Units

Repeats in this range are rare and represent approximately 1 to 2% of expanded alleles seen in HD testing programs. Some persons with repeats in this range develop HD and others live into their late 90s without evidence of the disease.[5,6] There is evidence that penetrance increases with increasing allele size in this range.

HD: Repeats of 40 Units or Larger

Currently, it is believed that all persons with repeats in the range of 40 or more will eventually develop HD. However, some individuals with repeats at the low end of this range are reported to exhibit initial symptoms at ages older than common life expectancy and thus there may be some reduced penetrance among carriers of 40 and 41 repeats.[7,8]

Recommendations on the Use of Genetic Testing.

Genetic testing for Huntington's disease is offered in three circumstances: Confirmatory and diagnostic testing, predictive testing, and prenatal testing.

Confirmation of diagnosis by direct gene testing may be warranted when a clinical diagnosis of HD has been made but the presence of an expanded Huntington CAG repeat has not been confirmed in an affected member of the family. Similarly, diagnostic testing may be performed for persons with a neurological disorder consistent with the HD diagnosis but absent family history because of early death of ancestors, non-paternity, or adoption.

Presymptomatic testing to determine the HD carrier status of individuals at risk for HD may be performed for persons who request this information. Because there is no medical intervention to delay onset or lessen the severity of the disease, presymptomatic testing should be done cautiously.[3,4,9] Often presymptomatic testing is sought when major life decisions are contemplated, such as marriage or childbearing.

Prenatal testing may be performed when one parent is known to carry the HD gene and the couple wants to determine the carrier status of the fetus. Genetic counseling to weigh the option of terminating the pregnancy of a fetus bearing the HD gene is crucial. In some instances, individuals at risk for HD may request a prenatal test when their carrier status is unknown. Tests that may reveal simultaneously that the parent and the fetus are HD gene carriers can be emotionally difficult. Sequential testing of the parent and then the fetus has the advantage of preventing some unnecessary prenatal testing when the parent is gene negative.

PARKINSON'S DISEASE AND PARKINSONIAN SYNDROMES

Thomas Gasser

Familial Parkinson's Disease

Until recently, the role of genetic factors in the etiology of Parkinson's disease (PD) has not been widely recognized. Today, it is well known that mutations in several genes are able to cause monogenically inherited forms of Parkinson's disease.

PARK1: Parkinson's Disease Caused by Mutations in the Gene for α-Synuclein

The discovery that mutations in the gene for α-synuclein can cause an early-onset form of PD with autosomal-dominant inheritance is particularly interesting in light of the fact that the α-synuclein protein is one of the major components of the histopathologic hallmark of PD, the Lewy body.[10] Only two mutations have been identified so far: one causing an amino acid exchange (threonine for alanine) at position 53 of the protein in an Italian and several Greek families,[11] and one substituting a proline for an alanine at position 30 in a German pedigree.[12] The phenotype resembles idiopathic PD both clinically and neuropathologically,[13] with the exception of an earlier age at onset (mean age at onset approximately 45 years).

Recommendations on the Use of Genetic Testing.

As mutations in this gene are exceedingly rare, sequencing is not routinely warranted in a clinical setting, but may be possible in exceptional cases for research purposes.

PARK2: Autosomal-Recessive Juvenile Parkinsonism

Mutations in the parkin gene on chromosome 6 have first been identified in Japanese patients with an autosomal-recessive syndrome of juvenile parkinsonism.[14] The clinical syndrome is that of L-dopa–responsive parkinsonism with early development of fluctuations and dyskinesias, but a relatively slow progression and a sustained good response to treatment. There may be dystonia at onset of the disease in some cases. In the few cases that have come to autopsy, severe degeneration of the substantia nigra is found, but no Lewy bodies, possibly indicating a molecular pathogenesis differing from that of idiopathic Parkinson's disease. Many different mutations, including exon deletions and point mutations have been identified. Mutations in the *parkin* gene appear to be much more frequent than those in α-synuclein. In a series of 73 pairs of affected siblings, parkin mutations have been identified in nearly 50% of families.[15] In sporadic patients, the prevalence of parkin mutations largely depends on the age at onset: While the majority of patients with onset under 20 years of age (>70%) and 25% of those with onset in the third decade carry parkin mutations, these are only rarely found in patients with an age at onset above 40.[15] However, in exceptional cases onset may be as late as 58.[16]

Recommendations on the Use of Genetic Testing.

Genetic testing can be offered in young-onset cases of L-dopa–responsive PD. However, the chance of detecting parkin mutations is probably only in the range of 2–5% in patients with onset under 40. It is much greater in those with onset under 30 and in those with a possible recessive inheritance (more than one affected sibling). Confirmation of this recessive form of PD may be helpful in genetic counseling, as it renders transmission to the subsequent generation very unlikely.

Other Forms of Inherited Parkinson's Disease

In other forms of familial parkinsonism (dominant: PARK3 on chromosome 2p13,[17] PARK4 on chromosome 4p,[18] and PARK8 on chromosome 12[19]; recessive: PARK6[20] and PARK7,[21] both on chromosome 1) no genetic testing is available as the respective genes have not yet been identified.

Sporadic Parkinson's Disease or Parkinson's Disease with Familial Clustering

The vast majority of cases with typical Lewy-body Parkinson's disease is clearly not inherited in a simple mendelian fashion. Although a large number of genetic risk factors has been studied in this population, none of them has so far been confirmed beyond doubt, so they cannot be used for risk-counseling in PD.

Recommendations on the Use of Genetic Testing.

No genetic testing is available at present.

Other Parkinsonian Syndromes

Progressive Supranuclear Palsy (PSP).

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterized by an akinetic rigid syndrome, dementia, and supranuclear gaze palsy. It occurs as a sporadic disorder in the vast majority of cases. Pathologically, straight filaments consisting of hyperphosphorylated MAPtau-protein ("microtubule-associated protein") are found in neurons. Interestingly, the great majority of patients with clinically probable PSP are homozygous for an extended haplotype of DNA-polymorphisms within and around the MAPtau gene.[22,23] It is hypothesized that these polymorphisms may be in linkage disequilibrium with another, as yet undetected, DNA sequence variation in the regulatory regions of the tau gene, altering its expression pattern and thereby promoting aggregation of tau in straight filaments.

As this haplotype is found in the homozygous state also in a significant percentage of age-matched normal individuals, it can certainly not be the only determinant of tau pathology. However, lack of homozygosity for this haplotype practically excludes the diagnosis of "pure" PSP.

Homozygosity for this haplotype has also been found in cases with corticobasal degeneration (CBD), a disorder which is also associated with abnormal tau-accumulation, further strengthening the suspected etiologic link between these two disorders.

Recommendations on the Use of Genetic Testing.

As the presence of the PSP-associated haplotype is not helpful in the diagnosis of an individual case of PSP, genetic analysis should be restricted to a research setting. No clinically useful genetic test can be offered to patients.

Frontotemporal Dementia with Parkinsonism Linked to Chromosome 17 (FTDP-17).

After Alzheimer's disease, frontotemporal dementia (FTD) is the most common neurodegenerative dementia.

TABLE 1. *Hereditary ataxias with autosomal recessive inheritance*

Disorder	Symbol	Locus	Gene	Mutation	Ref.
Friedreich's ataxia	FRDA	9q13-21.1	Frataxin	Trinuc/Pm	29
Ataxia telangiectasia	AT	11q22-23	PI3-kinase	Pm	32
Ataxia with oculomotor apraxia	AOA	9p13.3	Aprataxin	Pm, Ins, Del	33, 34
Autosomal recessive spastic ataxia of Charlevoix-Saguenay	ARSACS	13q11	Sacsin	Pm	35
Abetalipoproteinemia	ABL	4q22-24	Microsomal triglyceride transfer protein	Pm	37
Ataxia with vitamin deficiency	AVED	8q13.1-13.3	α-Tocopherol transfer-protein	Pm	38
Refsum's disease	PHAX	10pter-p11.2	Phytanoyl-CoA hydroxylase	Pm, Del, Ins	39
Cerebrotendinous xanthomatosis	CTX	2q33-qter	Sterol 27-hydroxylase	Pm	40
Spinocerebellar ataxia, non-Friedreich	SCAR1	9q34	Unknown	Unknown	41, 42
Spinocerebellar ataxia with blindness and deafness	SCABD	6p23-21	Unknown	Unknown	41
Infantile onset spinocerebellar ataxia	IOSCA	10q24	Unknown	Unknown	43

AD, autosomal dominant; AR, autosomal recessive; Del, deletion; Ins, insertion; mat, maternal (mitochondrial) transmission; Pm, point mutation; Trinuc, trinucleotide-repeat expansion; X, X-chromosomal.

FTD is neuropathologically heterogeneous, and only about 20% of patients with this disorder have the classic, argentophilic, intraneuronal inclusions (Pick bodies). Clinically, the FTD phenotype is defined as a neurobehavioral entity with a unique lobar, topographic distribution that is accompanied by tau pathology in most cases.[25] About half of FTD is inherited, usually in an autosomal dominant fashion. Only a small percentage (<10%) of patients with this syndrome have been *linked to chromosome 17* (FTDP-17). Mutations in the gene for MAPtau on chromosome 17 have been identified in some of these families.[26] Clinical variability is present in some pedigrees as illustrated in a family described under the name of pallido-ponto-nigral degeneration that featured extrapyramidal features in the form of L-dopa unresponsive parkinsonism.[27,28]

Recommendations on the Use of Genetic Testing.

On cases with a typical phenotype of frontotemporal dementia with or without parkinsonism and a positive family history, mutational analysis can be helpful for genetic counseling purposes. At present, it is offered within a research setting only. Genetic counseling before the test needs to be performed to weigh the possible benefits and risks for the individual and the family, in the absence of any therapeutic options in this disorder (see also General Overview).

AUTOSOMAL-RECESSIVE ATAXIAS

Thomas Klockgether

The recessive ataxias are a heterogeneous group of autosomal recessively inherited disorders that are characterized by progressive ataxia. In general, disease onset is in childhood or adolescence. However, milder variants with later disease onset have been described in almost all disorders. Therefore, recessive ataxias have to be considered in the work-up of patients with adult-onset sporadic ataxia of unknown origin.

In eight disorders (Friedreich's ataxia, ataxia telangiectasia, autosomal recessive ataxia with oculomotor apraxia, autosomal recessive spastic ataxia of Charlevoix-Saguenay, abetalipoproteinemia, ataxia with isolated vitamin E deficiency, Refsum's disease, and cerebrotendinous xanthomatosis), the affected gene and the causative mutations have been identified, while in three disorders (autosomal recessive ataxia linked to chromosome 9q, autosomal recessive ataxia with hearing impairment and optic atrophy, infantile onset spinocerebellar ataxia), only the chromosomal gene locus is known. The umbrella term "early onset cerebellar ataxia (EOCA)" is used to denote those recessive ataxias in which neither gene mutations nor chromosomal loci are known (Table 1).

The only recessive ataxia, in which diagnostic genetic testing is routinely used, is Friedreich's ataxia (FRDA), a trinucleotide repeat disorder. In most other recessive ataxias, allelic heterogeneity makes routine molecular genetic testing difficult. However, simple and reliable biochemical tests are available for several recessive forms.

Friedreich's Ataxia (FRDA)

FRDA is the most frequent recessive ataxia. It is characterized by onset in adolescence, progressive gait and limb ataxia, dysarthria, lower limb areflexia, loss of proprioception, and cardiomyopathy. Ninety-six percent of FRDA patients are homozygous for a GAA repeat

expansion in the first intron of the X25/frataxin gene.[29] Normal repeat length ranges from 6 to 36 units, whereas expanded alleles have 90 to 1,300 repeats. Age of onset is inversely correlated with the size of the shorter allele.[30] The remaining patients are heterozygous for the GAA expansion and a point mutation in the frataxin gene. Point mutations include truncating and missense mutations.[31] Systematic clinical studies showed that 20 to 30% of patients homozygous for the GAA repeat expansion have atypical clinical features with disease onset after the age of 25 years or preservation of muscle reflexes.[30]

Recommendations on the Use of Genetic Testing.

Genetic testing for FRDA is widely available. The test is useful to confirm diagnosis in patients with the typical phenotype of FRDA. The length of expansion should not be used for individual prognosis, given the large scattering of points along the correlation curve. Genetic testing for FRDA can also be useful as part of a diagnostic screen in patients with otherwise unexplained progressive ataxia if family history is compatible with autosomal recessive inheritance. Finding of a heterozygous GAA expansion in a symptomatic individual suggests the presence of a point mutation on the second allele. A prenatal test can be offered to couples who have already one child suffering from FRDA. Genetic counseling to weigh the option of terminating the pregnancy of a fetus bearing the FRDA mutation is crucial (see also General Overview).

Ataxia Telangiectasia (AT)

AT is an autosomal recessively inherited multisystem disorder characterized by cerebellar ataxia with an onset in early childhood, oculocutaneous teleangiectasias, a high incidence of neoplasia, radiosensitivity, and recurrent infections. The gene affected in AT, ATM, encodes a member of the phosphoinositol-3 kinase family involved in cell cycle checkpoint control and DNA repair.[32] More than 200 distinct mutations distributed over the entire gene have been reported suggesting that most patients carry unique mutations.

Recommendations on the Use of Genetic Testing.

Because genetic testing requires sequencing of the entire ATM gene, it should be restricted to cases in which the diagnosis cannot be made by biochemical tests. The most useful test is determination of serum α-fetoprotein, which is elevated in 90% of AT patients. In addition, radiosensitivity testing in cultured fibroblasts is offered by specialized laboratories.

Autosomal Recessive Ataxia with Oculomotor Apraxia (AOA)

AOA is a rare, autosomal recessively inherited ataxia caused by various mutations in a gene coding for a novel protein named aprataxin. The neurological presentation of AOA is variable. The gene has been simultaneously found by two research groups, one studying Portuguese families with an AT-like neurological phenotype including progressive ataxia, oculomotor apraxia, and peripheral neuropathy, and another studying Japanese families with ataxia and hypalbuminemia.[33,34] In contrast to AT, neoplasias and recurrent infections are not increased in AOA.

Recommendations on the Use of Genetic Testing.

Currently, genetic tests for AOA are not routinely offered.

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS)

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an autosomal recessive disorder clinically characterized by progressive ataxia and spasticity. Molecular genetic studies in an isolated population in the Charlevoix and the Saguenay regions of Québec, Canada, identified causative mutations in a novel gene encoding a large protein named sacsin containing a heat-shock domain.[35] The most frequent mutation accounting for more than 90% of all mutations is a deletion leading to protein truncation. Linkage to the same locus was established in a Tunisian family with a similar phenotype.[36] At present, it is not known how frequent ARSACS is outside the Charlevoix and the Saguenay regions of Québec, Canada.

Recommendations on the Use of Genetic Testing.

Currently, genetic tests for ARSACS are not routinely offered.

Abetalipoproteinemia

Abetalipoproteinemia is an autosomal recessively inherited disorder characterized by onset of diarrhea soon after birth and slow development of ataxia, limb weakness, disturbed sensation, and retinal degeneration thereafter. Abetalipoproteinemia is caused by mutations of the gene encoding a subunit of a microsomal triglyceride transfer protein.[37] The mutations include point mutations, deletions, and insertions. As a consequence, circulating apolipoprotein-B–containing lipoproteins are almost completely missing, and the patients are unable to absorb and transport fat and fat-soluble vitamins. The neurological symptoms are due to vitamin E deficiency.

Recommendations on the Use of Genetic Testing.

Genetic testing for abetalipoproteinemia is not routinely used. The diagnosis is made by lipid electrophoresis showing low serum cholesterol (<70 mg/dl) and nearly absent very low-density lipoproteins. In addition, blood smears show acanthocytosis, and serum vitamin E levels are reduced. However, these latter findings are not specific for abetalipoproteinemia.

Ataxia with Isolated Vitamin E Deficiency (AVED).

Ataxia with isolated vitamin E deficiency (AVED) is an autosomal recessively inherited disorder with a phenotype resembling FRDA. AVED patients carry homozygous mutations of the gene encoding α-tocopherol transport protein, a liver-specific protein that incorporates vitamin E into very low-density lipoproteins.[38] As a consequence, vitamin E is rapidly eliminated.

Recommendations on the Use of Genetic Testing.

Genetic tests are of no practical importance. The diagnosis is made by determining serum vitamin E levels.

Refsum's Disease

Refsum's disease is due to mutations in the gene encoding phytanoyl-CoA hydroxylase that is involved in the α-oxidation of phytanic acid.[39] The clinical phenotype of Refsum's disease is caused by accumulation of phytanic acid in body tissues. Clinically, Refsum's disease is characterized by ataxia, demyelinating sensorimotor neuropathy, pigmentary retinal degeneration, deafness, cardiac arrhythmias, and ichthyosis-like skin changes.

Recommendations on the Use of Genetic Testing.

Genetic tests are of no practical importance. The diagnosis is made by determining serum phytanic acid levels.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis is an autosomal recessive lipid storage disorder with accumulation of cholestanol and cholesterin in various tissues. The disorder is due to different mutations (substitutions, deletions, and insertions) of the gene encoding cholestanol 27-hydroxylase.[40] The clinical syndrome includes xanthomatous swelling of the tendons, cataracts, and a slowly progressive neurological syndrome including ataxia, pyramidal signs, and cognitive decline.

Recommendations on the Use of Genetic Testing.

The diversity of mutations make genetic testing difficult. However, common gene mutations have been iden-

tified in certain populations. The principal way to establish a diagnosis of cerebrotendinous xanthomatosis is determination of serum cholestanol.

Autosomal Recessive Ataxia Linked to Chromosome 9q

Recently, linkage to chromosome 9q was demonstrated in a consanguineous Japanese family with ataxia associated with elevated levels of serum creatine kinase, γ-globulin, and α-fetoprotein.[41] Another family with the clinical phenotype of ataxia with oculomotor apraxia was mapped to the same chromosomal region.[42] A genetic test for this disorder is not available.

Autosomal Recessive Ataxia with Hearing Impairment and Optic Atrophy

Linkage to chromosome 6p was demonstrated in an Israeli family with early-onset recessive ataxia. Patients subsequently developed hearing impairment and optic atrophy.[41] A genetic test for this disorder is not available.

Infantile Onset Spinocerebellar Ataxia (IOSCA)

IOSCA is an early onset recessive ataxia linked to a locus on chromosome 10q that has been described in Finnish families. The disease manifests around the age of one year as acute or subacute clumsiness, athetoid movements in hands and face, hypotonia, and loss of deep tendon reflexes in the legs. Ophthalmoplegia and a sensorineural hearing deficit are found by school age, sensory neuropathy and optic atrophy by the age of 10 to 15 years, and female hypogonadism and epilepsy by the age of 15 to 20 years.[43] A genetic test for this disorder is not available.

Other Forms of Early Onset Cerebellar Ataxia (EOCA)

EOCA is used to denote those ataxias with an onset before the age of 25 years in which the etiology is unknown. Apart from cerebellar ataxia, patients may present with a variety of additional symptoms including retinal degeneration (Hallgren syndrome), hypogonadism (Holmes syndrome), optic atrophy (Behr syndrome), cataracts and mental retardation (Marinesco-Sjögren syndrome), and myoclonus (Ramsay Hunt syndrome). Genetic or biochemical tests for these disorders are not available.

AUTOSOMAL-DOMINANT CEREBELLAR ATAXIAS

Alexandra Dürr

Autosomal dominant cerebellar ataxias are genetically and clinically heterogeneous. Clinical heterogeneity is

TABLE 2. *Classification of autosomal dominant cerebellar ataxias*

Gene	Locus	Proportion of SCAs	Pathological repeat sizes	Particularities	Ref.
Genes identified					
SCA1	6p23	5–40%	39–83		44
SCA2	12p24	10–40%	32–77		45
SCA3	14q32	11–84%	54–89	Machado-Joseph disease	46
SCA6	19p31	1–16%	20–33	α1 subunit calcium channel	47
SCA7	3p12	5–8%	37–306	Ataxia and progressive macular dystrophy	48
SCA10	22q13	3 families	ATTCT[a]	Ataxia and epilepsy	49
SCA12	17	2 families	55–78[a]	PPP2R2B gene	50
DRPLA	14	Rare	39–83	Atrophin	51
TBP (SCA 17)		Rare	44–63	Very severe phenotype	52
Genes not yet identified					
SCA4	16q	1 family			53
SCA5	11cen	2 families			54
SCA8	13q21	1 family	>107[a]	CTG repeat: pathological or polymorphism?	55
SCA11	15q	1 family			56
SCA13	19	1 family		Ataxia and mental retardation	57
SCA14	19	1 family			58
SCA16	8q	1 family		Ataxia and head tremor	59

[a]Non-coding repeat.

reflected by the pattern of atrophy on cerebral imaging, which varies from typical olivo-ponto-cerebellar atrophy to isolated atrophy of the cerebellum. The mapped genes are designated SCA (spinocerebellar ataxia) 1 to 8, SCA10 to 17, and DRPLA (dentatorubropallidoluyisian atrophy). SCA17 is a complex syndrome of cerebellar ataxia and intellectual deterioration associated with a de novo expansion of a CAG repeat in the TATA box binding protein (TBP) gene. Nine genes have been identified, reflecting a marked genetic heterogeneity (Table 2). Except for SCA8, in which the causative mutation remains a matter of debate, the same molecular mechanism appears to underlie the disease process in all SCAs: the expansion of a CAG trinucleotide repeat in the coding sequence of the involved genes resulting in a polyglutamine expansion in the corresponding protein. SCA12 is an exception, as the gene harbors a trinucleotide expansion in the non-coding region (similar to Friedreich's ataxia or myotonic dystrophy).

The clinical and pathological heterogeneity that is found even among affected members of the same family makes accurate clinical diagnosis difficult. In addition, the clinical overlap among different SCAs makes prediction of the molecular origin impossible and emphasizes the usefulness of molecular analysis. However, each entity has particularities that are related to the gene involved, to the size of the expansion, and to the disease duration but often they are not specific enough to be clinically useful (Table 3). The relative frequency of the different SCAs varies markedly among countries, both within Europe and in other parts of the world, but SCA3 (Machado-Joseph disease) is the most frequent gene in most populations.

Pitfalls in Molecular Analysis

In most instances, there is a clear-cut difference in the size of normal and pathological alleles, which allows their unambiguous identification in molecular testing. However, there is some overlap at the SCA1 and SCA2 loci where normal repeats in the pathological range up to 44 and 34 units were observed, respectively. Fortunately, sequencing these large normal repeats should allow them to be distinguished from pathological expansions because large normal CAG repeats are interrupted, by one

TABLE 3. *Phenotype-genotype correlation in autosomal dominant cerebellar ataxias*

	CAG repeat expansion		
	Small	Medium	Large
SCA1		Cerebellar ataxia, increased reflexes	Amyotrophic lateral sclerosis-like
SCA2	Postural tremor	Cerebellar ataxia, decreased reflexes	Cerebellar ataxia, chorea, dementia (Huntington's disease–like)
SCA3	Axonal neuropathy, parkinsonism	Cerebellar ataxia, gaze-evoked nystagmus	
SCA6	Episodic ataxia-like	Pure cerebellar ataxia	
SCA7	Cerebellar ataxia without visual loss	Cerebellar ataxia, macular degeneration	Visual loss before cerebellar syndrome
SCA17		Cerebellar ataxia, dementia, chorea	Mental retardation, short stature

or more CAT in SCA1 and CAA in SCA2, whereas pathological ones are made of pure CAG repeats.

Recommendations on the Use of Genetic Testing.

Genetic counseling should accompany molecular testing in each patient and be offered to relatives after the identification of a SCA mutation.

1. Screening for CAG expansion in known genes will identify the responsible gene in more than 60% of the families with *autosomal dominant* cerebellar ataxia in a European population. This proportion varies in different populations: in Japan, for example, about 80% of all dominant SCAs are explained by identified genes. In some instances, the strategy for molecular testing can be guided by the frequency of the mutation in the population (Table 2) or by the clinical picture (Table 3). For instance, most Portuguese patients carry the SCA3/MJD mutation and most Italian cases are accounted for by SCA1 or SCA2. The relative prevalences of MJD/SCA3, SCA6, and DRPLA are significantly higher in Japanese (43%, 11%, and 20%, respectively) than in Caucasian patients (30%, 5%, and 0%, respectively). The occurrence of the different SCAs in various parts of the world has been found to correlate with the size of the respective CAG-repeat, from which pathologic expansions arise, in the populations in question.[60]

   Clinically, the association of cerebellar ataxia and vision loss is very specific of SCA7, other clinical clues are less helpful. When all known genes are excluded linkage analyses for other mapped loci can only be performed in very large families but this is not usually done in clinical practice.

2. In sporadic cases with adult onset the mutation responsible for Friedreich's ataxia is more frequent than those for the various SCAs. The frequency of isolated cases with known SCA mutations ranges from 2 to 7% depending on the population.[61] Most isolated cases, which turned out to be SCA, are explained by the following reasons: 1) censured history, because of early death of the transmitting parent, adoption or false paternity, 2) still asymptomatic parent because of anticipation (particularly in SCA7), 3) false diagnosis in affected relatives not verified by clinical examination (multiple sclerosis for instance), or 4) de-novo mutation (SCA7, TBP).

3. Presymptomatic testing for unaffected at-risk individuals and prenatal testing can be offered in families with identified mutations. As shown by the 10 years experience of presymptomatic testing in Huntington's disease and because of the obvious similarities be-

tween the two conditions (absence of prevention or treatment), intensive pre-test and post-test counseling and psychological support is necessary as stated above.

4. Exclusion of the SCA mutations and loci in familial cerebellar ataxia does not exclude the presence of a mutation in an as yet unknown gene. Therefore, negative genetic testing does not rule out autosomal dominant transmission and requires appropriate genetic counseling.

WILSON DISEASE

Thomas Gasser

Wilson disease is a disorder of copper metabolism that can present with neurological, hepatic, or psychiatric disturbances, or a combination thereof. Neurological presentations include movement disorders (tremor, dystonia, dysarthria, bradykinesia, choreoathetosis). Psychiatric disturbances include depression, disorganization of personality, and, occasionally, intellectual deterioration, while hepatic involvement manifests as acute and chronic hepatitis leading to cirrhosis and liver failure. The worldwide prevalence of Wilson disease is estimated to be of the order of 30 per 1 million, with a gene frequency of 0.56% and a carrier frequency of 1 in 90.

Wilson disease is caused by mutations in the gene for a copper-transporting p-type ATPase, called ATP7B,[62,63] located on chromosom13q14-q21. Based on experiments in animal models, it is likely that the ATP7B protein may function in the copper transport coupled with the synthesis of ceruloplasmin in the Golgi apparatus.[64] Its function is essential for biliary excretion of copper.

The ATP7B gene is a large gene with an open reading frame of more than 10,000 bp. More than 170 mutations have been described so far, most being point mutations or small deletions (see mutation database online: www.medgen.med.ualberta.ca/database.html).

There is a rough relationship between genotype and phenotype: mutations leading to a complete abolition of ATP7B function (early stop mutations, mutations in highly conserved and functionally important regions) lead to an early and predominantly hepatic dysfunction, whereas point mutations in less important regions of the gene are associated with later onset and a predominance of neurological and psychiatric symptoms.[65] There is only one mutation that occurs with a fairly high frequency in a mixed Caucasian population, H1059Q. A mean age of onset of 20 to 22 years in patients homozygous for this mutation has been described.[66,67]

Generally, the diagnosis of WD in a symptomatic individual relies upon demonstration of abnormal copper

indices, including low serum ceruloplasmin, high urinary copper and/or increased hepatic copper content, and the demonstration of a Kayser-Fleischer ring of the cornea.

Recommendations on the Use of Genetic Testing.

Mutational analysis of the ATP7B gene is available on a limited basis only. Some laboratories offer detection of the H1096Q mutation and a few others of the more common sequence alterations. Due to the large size of the gene, however, it is usually not feasible to sequence the entire coding region. Therefore, failure to detect one of the common mutations does not rule out the diagnosis and is not helpful for management and genetic counseling.

"Indirect" genetic diagnosis (see *General Overview*) can be considered for the early diagnosis and treatment of at-risk sibs of an individual affected with Wilson disease. Markers within and flanking the gene must be typed to exclude recombinations. If the markers are informative (i.e., they allow to discriminate between the two parental chromosomes), it is possible to determine whether a clinically healthy sibling of an affected carries one or both of the affected chromosomes. This information allows the institution of early treatment in homozygotes and genetic counseling of the heterozygous carrier (at an estimated carrier rate of 1/90 in the general population, the risk that a carrier would marry another carrier and have an affected child is one in 360). Prenatal testing is possible when linkage studies are informative. In this case, careful counseling again is crucial to discuss different options, including the termination of a pregnancy on the basis of genetic testing in WD, particularly considering the potential treatability of the disease when diagnosed early.

ESSENTIAL TREMOR

Joseph J. Higgins

ET is one of the most common neurological conditions in humans with an overall prevalence ranging between 4.1 to 39.2 cases per 1,000 persons.[68] Although the disorder is prevalent, little is known about its pathogenesis. Studies using positron emission tomography in humans provide evidence for a central nervous system etiology for ET by demonstrating an increase in glucose utilization of the olivocerebellar pathway.[69]

Most cases of ET are familial,[70,71] and most often described as an autosomal dominant trait with high, but not full penetrance.[72,73]

Loci in families with "pure" ET have been mapped to the short arm of chromosome 2 and the long arm of chromosome 3.[74–76] The locus on chromosome 2 (*ETM*) was initially identified in a large American family of

Czech descent and subsequently confirmed in three other American families. The locus on chromosome 3 (*FET1*) was found in 16 small Icelandic families affected with a similar ET phenotype.[76] These studies suggest that there is nonallelic genetic heterogeneity causing the "pure" ET phenotype.

Recommendations on the Use of Genetic Testing.

Because the genes that cause ET are not known, genetic testing for ET is not currently available. However, genetic research studies are being conducted in families with dominantly inherited ET.

PRIMARY TORSION DYSTONIA

Susan B. Bressman

There are many genetic causes for dystonia and they are divided into two categories: primary (or idiopathic) and secondary (see Table 4).[77] Secondary dystonia has always been recognized as a broad category containing many different disorders, whereas primary dystonia initially denoted a unitary state of pure dystonia of unknown (but possibly genetic), origin. To diagnose primary dystonia required: 1) no exogenous or acquired etiology (e.g., trauma, neuroleptic intake, birth asphyxia); 2) no suspicion of a degenerative or inherited disorder with associated pathological or neurochemical changes (e.g., Hallervorden Spatz, Wilson's disease, Parkinson's disease); and 3) aside from tremor, no physical/neurological signs other than dystonia. Although these criteria continue to distinguish primary from secondary dystonia, primary dystonia is no longer a single entity, and at least to some extent it is no longer a diagnosis of exclusion. As loci and genes are identified, and their functions clarified, the distinction between primary and secondary dystonia is blurring. Primary dystonia as a group of disorders, many of genetic etiology, is emerging.

The clinical spectrum of primary dystonia is remarkably variable, but there is a clustering of key clinical features suggesting distinct genetic subgroups. The age at onset distribution is bimodal, with a peak at age 9 (early onset) and 45 (late onset), divided by a nadir at age 27.[78] Moreover, there is a relationship between the age at onset of symptoms, body region first affected, and clinical progression of signs. When primary dystonia begins in childhood or adolescence, it often starts in a leg or arm, and then progresses to involve multiple body regions; when it begins in adult years, symptoms first involve the neck, cranial, or arm muscles, and dystonia tends to remains localized.[79]

TABLE 4. *Molecular classification dystonia*

Gene	Locus	Particularities	Ref.
DYT1	9q34	Early limb-onset primary torsion dystonia; autosomal dominant with 30% penetrance; gene encodes torsinA; all identified mutations are a GAG deletion	80
DYT2	?	Autosomal recessive in Gypsies	
DYT3	Xq13.1	X-linked dystonia parkinsonism (known as *XDP* or *Lubag*); almost all due to founder Filipino mutation; young adult-onset, cranial (including larynx/stridor) and limb dystonia, parkinsonism develops (or at onset) with shuffling, drooling	108
DYT4	?	Whispering dysphonia in Australian family; autosomal dominant	109
DYT5	14q22.1	Childhood-onset dopa-responsive dystonia (*DRD*) and parkinsonism; autosomal dominant with sex influenced reduced penetrance (higher in girls); gene encodes GTP cyclohydrolase1, many different mutations	95
DYT6	8p	Adolescent and early adult-onset, mixed phenotype with limb, cervical and cranial onset and both limited and generalized spread; thus far only found in Mennonite families; autosomal dominant reduced penetrance	91
DYT7	18p	Late-onset primary cervical dystonia in North German families, autosomal dominant with reduced penetrance	92
DYT8	2q	Paroxysmal non-kinesigenic choreoathetosis (PNKC); autosomal dominant	110
DYT9	1p	Episodic choreoathetosis with spasticity (CSE), autosomal dominant	93
DYT10	16p11	Paroxysmal kinesigenic dystonia (PKC)	111
DYT11	7q21	Myoclonus-dystonia, autosomal dominant childhood-onset dystonia (esp. limbs and neck) and myoclonus (esp. neck, shoulders, face), often better with alcohol, caused by mutations in the gene for ε-sarcoglycan	107
DYT12	19q	Rapid-onset dystonia-parkinsonism (RDP), autosomal dominant with reduced penetrance	112
DYT13	1p36	Adult-onset dystonia with predominant cervical and upper-limb distribution	113

DYT1 and Early-Onset PTD (Also Termed Dystonia Musculorum Deformans)

One form of early-onset primary dystonia (DYT1), which is transmitted in an autosomal dominant fashion with reduced (30–40%) penetrance, is caused by the deletion of one of a pair of GAG codons in a gene on chromosome 9q34, called TorsinA.[80] This is the only disease mutation in this gene identified to date. It has been found in families of diverse ethnic background,[81–84] and analyses of haplotypes indicate that deletions originated from multiple independent mutation events.

The clinical expression of the DYT1 GAG deletion is generally similar across ethnic groups.[82,83,85,86] The great majority of people with dystonia due to the DYT1 GAG deletion have early onset and all clinically ascertained cases reported to date have onset before age 26 years. One or more limbs are almost always affected and over 95% have an affected arm.[85] The DYT1 GAG-deletion is more important in the Ashkenazi population, where it accounts for about 90% of early limb-onset cases, due to a founder effect; this compares with non-Jewish people, where only 50–65% of early limb-onset PTD has the mutation.[80,82,86]

Recommendations on the Use of Genetic Testing.

Because of the reduced penetrance and variable expression of primary dystonia, with mild cases going undiagnosed, it is not uncommon to obtain a negative family history. Based on current findings it is not unreasonable to assume a genetic etiology for most early-onset primary dystonia, regardless of family history. Many cases (probably ~50%) will be due to DYT1.

Genetic testing is commercially available and should be considered the first diagnostic test to apply to: 1) all PTD patients, whether Ashkenazi or non-Jewish, with onset before the age 26 years and 2) PTD patients with later onset who have a related family member with early (<26 years) onset.[85] The specificity of using age 26 as a cut-off is higher in Ashkenazi Jews (63%) than non-Jews (43%); further, specificity can be greatly increased by restricting testing to those with limb-onset. However, sensitivity then decreases to about 95%. Genetic counseling, prior to molecular testing, has to take these limitations into account.

Late-Onset PTD

Late-onset PTD is genetically more complex than early-onset. Like early-onset primary dystonia, late-onset, focal, or cervical-cranial primary dystonia also may be inherited in an autosomal dominant fashion.[87–90] However, unlike early-onset dystonia, most studies show that penetrance is even more reduced (about 12–15% compared to 30% for early-onset). Alternatively, penetrance may be higher in a genetic subset with the remainder being non-genetic.

Two additional PTD loci have been mapped: DYT6 on chromosome 8 was identified in two families of Mennonite and Amish origin.[91] The phenotype in these families is "mixed" in that age-at-onset is relatively early (mean, 18 years; range, 6–38 years), but unlike most early-onset

primary dystonia, the cervical or cranial muscles are affected first in about one half.

Another locus (DYT7) was mapped in a Northwest German family affected primarily with late-onset torticollis, although mild facial and arm involvement was noted in one affected, as was spasmodic dysphonia.[92] The DYT7 gene localizes to a 30 cM region on chromosome 18p between D18S1153 and 18pter.[92,93] The extent to which DYT6 and DYT7 account for adult and cervical/cranial-onset primary dystonia remains unclear as there is evidence indicating other as yet unmapped loci.[94]

Recommendations on the Use of Genetic Testing.

The genetic contribution for most adult-onset PTD remains to be clarified and genetic counseling for the adult-onset group needs to reflect this. At present, there is no testing for PTD loci other than DYT1, although in sufficiently large families linkage to DYT6 or DYT7 may be performed on a research basis.

Dopa-Responsive Dystonia

A rarer variant of primary dystonia, *dopa-responsive dystonia* caused by point-mutations in the gene for GTP-cyclohydrolase I (GCHI) in the majority of cases.[95] Again, the phenotype is usually characterized by a childhood onset dystonia, affecting the extremities first, but rarely, craniocervical dystonia may be the only manifestation. As a large number of different mutations have been described that are scattered over the entire gene (and could not even be detected in all cases within the coding region), the practical role of molecular diagnosis is limited. Fortunately, a suspicion of dopa-responsive dystonia can usually be confirmed by the excellent response to L-dopa treatment, so that molecular analysis is frequently not necessary.

A recessive form of dopa-responsive dystonia has been described in patients with a genetic deficiency of tyrosine-hydroxylase (TH).[96,97] From the few cases that have been described in the literature, the phenotype appears to differ considerably from that in dopa-responsive dystonia caused by GCH-1 mutations, and includes hypokinetic-rigid symptoms[98] and spastic paraplegia[99] beginning in infancy.

Myoclonus–Dystonia Syndrome

Myoclonus–dystonia syndrome (MDS, DYT11) is an autosomal-dominant disorder characterized by bilateral, alcohol-sensitive myoclonic jerks, involving predominantly the arms and axial muscles. Dystonia, usually torticollis and/or writer's cramp, occurs in most, but not all affecteds, and may occasionally be the only symptom of the disease.[100,101] In addition, patients often show prominent psychiatric abnormalities, including panic attacks and obsessive-compulsive behavior.[102,103] In the majority of MDS families, the disease is linked to a locus on chromosome 7q21,[104–106] and different heterozygous loss-of-function mutations in the gene for ε-sarcoglycan, which maps to this area, have been identified.[107] Penetrance of the mutations is reduced, particularly if the disease allele is inherited from the mother, suggesting a maternal imprinting mechanism.[107]

Recommendations on the Use of Genetic Testing.

Genetic testing for MDS is presently available only on a research basis.

Other Forms of Dystonia

In other forms of dystonia, such as the *paroxysmal dystonias* or "*rapid-onset dystonia–parkinsonism,*" genes have been mapped but not cloned, and molecular diagnosis is not available.

OTHER GENETIC DISEASES ASSOCIATED WITH A VARIETY OF MOVEMENT DISORDERS

Thomas Gasser

Genes for an increasing number of other inherited diseases associated with a variety of movement disorders, which do not easily fit into one of the above categories, but may nevertheless represent important entities, are being mapped and cloned.

Neurodegeneration with Brain-Iron Accumulation Type 1

Neurodegeneration with brain-iron accumulation type 1 (NBIA-1, formerly called Hallervorden-Spatz syndrome) is an autosomal recessive disorder, usually presenting during childhood or early adolescence with a complex movement disorder with elements of dystonia, spasticity, and parkinsonism. Progressive dementia and epileptic seizures are also a part of the clinical picture. Characteristic iron accumulation in the basal ganglia, visualized as hypointensities on MR, is seen. The gene has been mapped to chromosome 20, and has recently been identified as the gene for pantotenate kinase 2 (PANK2), encoding a crucial enzyme of coenzyme A-synthesis. Interestingly, the associated phenotype appears to be broader than typical NBIA-1, as several cases with atypical presentations or later age of onset have been found to carry mutations.[114]

Another complex neurodegenerative phenotype that is being unraveled by cloning the responsible genes is neuroacanthocytosis. This syndrome is characterized by

a characteristic thorn-like appearance of red blood cells ("acanthocytes") and a progressive neurodegeneration, usually associated with a variety of extrapyramidal symptoms. An X-linked form, McLeod syndrome, is caused by loss-of-function mutations in a gene encoding a membrane protein (XK-protein), which is strongly expressed in erythrocytes and brain tissue.[115] An autosomal recessive form has been mapped to chromosome 9 and is caused by mutations in the gene for chorein. The gene product is possibly involved in the intracellular transport of proteins. Routine diagnosis is complicated by the fact that this is a huge gene, comprising 73 exons.[116]

A much larger number of genes associated with movement disorders undoubtedly still await discovery, providing both opportunity and challenge to the movement disorders specialist.

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