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Clinical Aspects of CAG Repeat Diseases

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Seven neurodegenerative disorders are known to be caused by unstable expansions of the trinucleotide CAG within human genes, and more will be discovered in the coming years. These disorders share some clinical similarities, as well as some differences, which are summarized here. These diseases have unusual clinical genetic properties related to the dynamic nature of CAG repeat expansions, including instability of the repeat expansion in meiosis, particularly male meiosis; a strong correlation between onset age and size of the repeat expansion; anticipation (earlier disease onset in succeeding generations); new mutations arising from unstable, mutable alleles with a high-normal CAG repeat number; and reduced penetrance for alleles in the low-affected range. Much more remains to be learned about the molecular biology and clinical pathophysiology of this new class of genetic diseases.

Introduction

The CAG repeat diseases are a fascinating group of neurogenetic disorders whose pathophysiology is only beginning to be understood. Seven diseases caused by expansion of intragenic CAG repeat sequences have been identified since 1991, and at least an equal number will doubtless be revealed in the next five years. Many tenets of classical Mendelian genetics have already been rewritten in the last six years because of what has been learned about the nature and behavior of these "dynamic mutations", and more surprises are on the way. Although much remains to be learned about the mechanisms of instability, mutability, and pathophysiology of CAG repeat sequences, the careful molecular genetic and clinical study of patients with these disorders has already led to some clinically important insights. The clinical features of the seven CAG repeat diseases are summarized below, along with aspects of the available molecular genetic data that have clinical relevance. While the clinical and molecular genetic similarities among these disorders allow them to be classified together, it is the subtle differences between them that will ultimately be the most interesting and challenging to explain.

The seven currently known CAG repeat disorders are Huntington disease (HD), dentatorubropallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA, Kennedy's disease), and spinocerebellar ataxias types 1,2,3, and 6 (SCA1, SCA2, SCA3, SCA6). All of these are adult-onset neurodegenerative disorders. Anticipation, the earlier onset of symptoms in succeeding generations, is a common feature of most CAG repeat disorders. Based on the clinical observation of anticipation within large kindreds, a number of additional disorders are expected to be caused by CAG repeat expansions: spinocerebellar ataxias types 4,5, and 7, and the familial spastic paraplegias. The CAG repeat disorders comprise a subset of the larger group of trinucleotide repeat disorders, which also includes two fragile X syndromes of mental retardation (FRAXA and FRAXE), myotonic dystrophy, and Friedreich's ataxia. Although some of the known trinucleotide repeat disorders are multi-systemic, they all exert major or primary effects on the nervous system, suggesting that neurons are particularly susceptible to damage by these mutations. The main clinical, epidemiologic, and pathologic features of the seven disorders are summarized in Table 1.

CLINICAL DESCRIPTION OF THE CAG REPEAT DISEASES

Huntington disease

Huntington disease (HD) was the only one of the known CAG repeat diseases to be recognized clinically before 1900. First described in 1872 by Dr. George Huntington, after whom it was named, HD was the subject of 1,963 scientific publications in its first century (14), and over 3,000 publications in the last 25 years (Medline search, 1997). Two authoritative books (53,55) have been written on HD, and over 10,000 patients have been described worldwide. Like all of the CAG repeat diseases except SBMA, it is an autosomal dominant condition. HD has been reported in most major ethnic and racial groups; major epidemiologic studies have been reviewed succinctly by Harper (53). The prevalence is in the range of 3-7/100,000 in most European and North American populations, and appears to be somewhat lower (1/100,000 or less) in African

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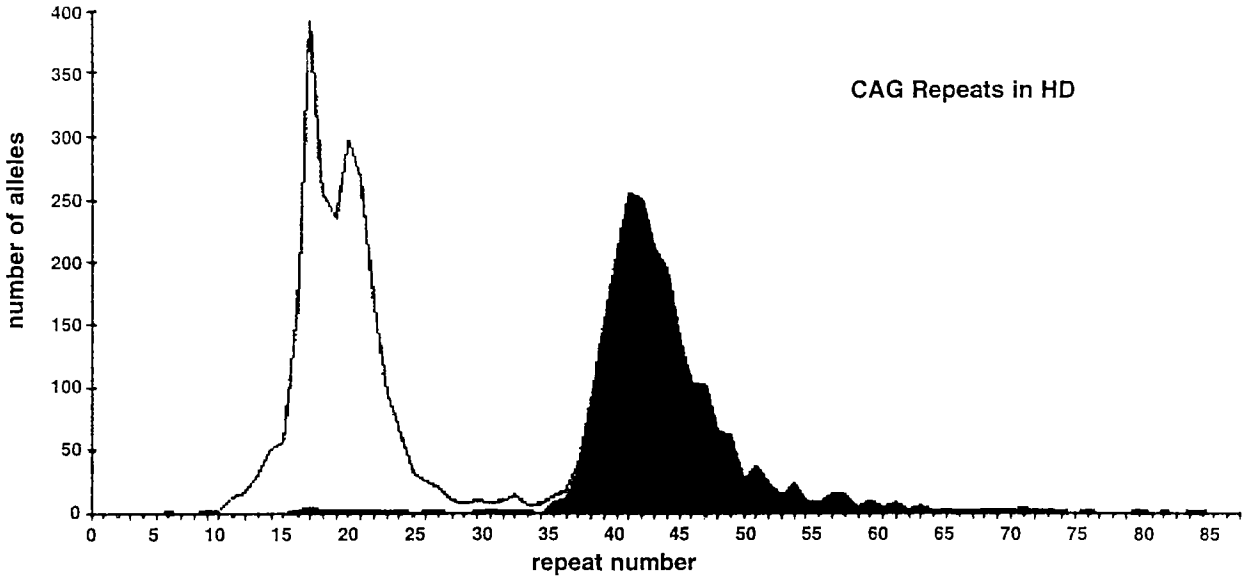

Figure 1. Reported normal and expanded CAG allele sizes for the seven CAG repeat disorders, displayed to emphasize the numbers of patients studied and the distribution of allele sizes. Alleles from control, unaffected, or lower alleles of affected subjects are shown in white; upper alleles of affected individuals are shown in black. **a.** Huntington disease (reprinted from (106), with permission) (N=2131 normal alleles, 2246 expanded alleles)

black and Asian populations. A few regions with high prevalence rates due to very large single kindreds or a founder effect are known (the Lake Maracaibo Venezuelan population, as well as populations in Tasmania, the Moray Firth region of Scotland, and others) (reviewed in 53).

Motor, cognitive, and behavioral dysfunction are the hallmarks of HD. The movement disorder includes both the presence of involuntary movements and impairment in the motor control of voluntary movements, the relative severity of which varies from individual to individual and during the course of the disease. There is impairment of the planning, initiation, sequencing, persistence, and completion of complex motor tasks, and eventually of simple movements. The involuntary movements are multifocal, irregular, and arrhythmic; they may be flowing and smooth (chorea), writhing or twisting (athetosis), abrupt and of high amplitude (ballismus), or less commonly, brief and simple (myoclonus). Involuntary movements with characteristics overlapping these categories are the rule rather than the exception. As the disease progresses, axial and limb rigidity and dystonic posturing accompany or replace chorea. Swallowing and speech become difficult and the patient becomes wheelchair- or bed-bound. As the disease runs its course, affected individuals become mute. Death can be due to HD itself, intercurrent infection (usually pneumonia), or unrelated causes (107).

The dementia of HD has been characterized as a "subcortical dementia", based on the clinical and pathological features which distinguish it from "cortical dementias" such as Alzheimer's disease (11). Cognitive dysfunction in the early stages of HD parallels many of the characteristics of the motor control disorder, in that there is difficulty with the "executive functions" of planning, initiating, sequencing, and persisting in activities or tasks. With disease progression, verbal learning, memory, and global measures of cognitive function (e.g., Wechsler Adult Intelligence Scale) are impaired.

The psychiatric disorder varies considerably, and may be the presenting symptom or group of symptoms in HD (53). A schizophrenia-like thought disorder has been reported in 3.4-12% of individuals. Depression is reported in 9-44% of affected individuals, and the suicide rate has ranged from 0.5-12.7%. Mania or hypomania, or other psychiatric diagnoses can also be present. In our experience, obsessive thought patterns or impulsive behavior are common and may be disabling. A small number of patients are diagnosed with sexual disorders, pathologic gambling, or eating disorders, and some patients have no discernable psychologic or psychiatric disturbance.

A fourth consistent feature of HD is weight loss. Most affected individuals eat ravenously but lose weight, particularly in the mid to late stages of the disease. The basis for weight loss has not been fully explained; it may relate in part to increased caloric requirements, psychosocial factors, or to the degenera-

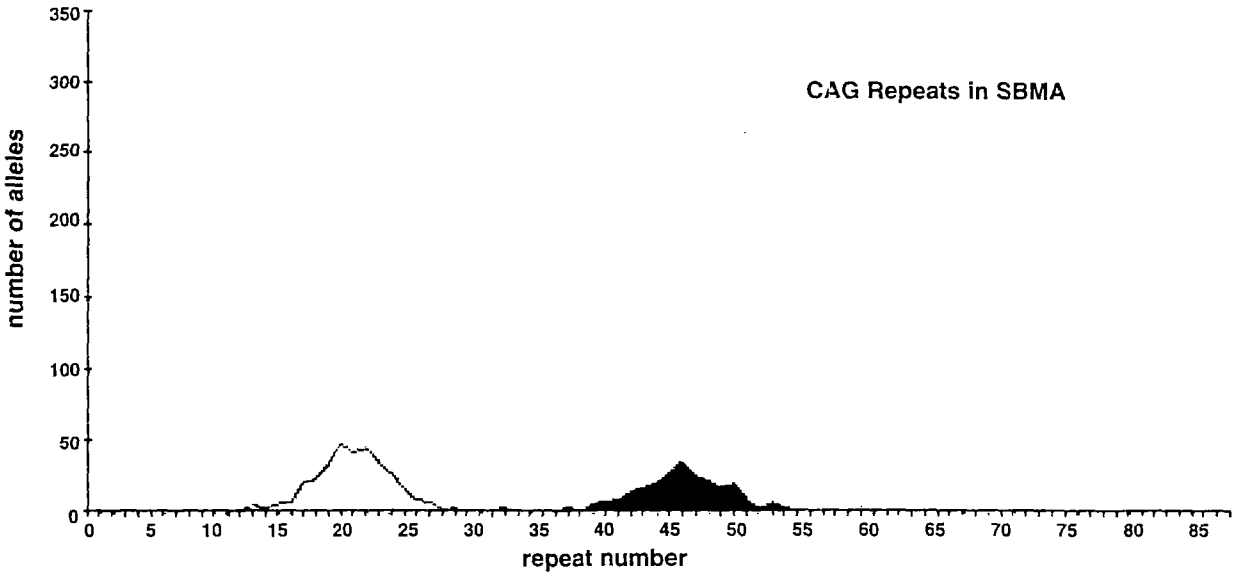

Figure 1. b. Kennedy disease (N= 322 normal alleles, 237 expanded alleles) (8, 10, 25, 26, 27, 33, 58, 64, 70, 79, 80, 89, 98, 104, 111, 120, 165, 178, 184, 186)

tive nervous system disease (75, 107, 110). It has been noted that patients who are overweight at the time of the diagnosis of HD progress more slowly than patients who are not, but whether this is a cause or effect of the disease is unknown (100).

HD affects the central nervous system only; no studies have reported primary disease effects on the peripheral nervous system or any other organ system. Clinically, HD does not directly affect sensory, visual, or linguistic cortical functions, or the function of brainstem nuclei or spinal cord. However, many patients develop evidence of pyramidal tract dysfunction as the disease progresses (hyperreflexia, extensor plantar responses, clonus, and spasticity). Occasional affected individuals, particularly children, have clinical or radiologic evidence of cerebellar abnormality (ataxia, cerebellar atrophy). Finally, seizures or epilepsy are seen more commonly in individuals with HD than in the general population, affecting up to 30% of children with juvenile-onset HD, and 1-3% of individuals with adult-onset HD (compared to a general population risk of 0.35-0.62%).

The average age of onset of symptoms in HD is 35-40 years. Symptoms begin insidiously, making the exact determination of onset problematic; for research purposes, disease onset is commonly defined either as the time that motor symptoms began, or as the time of the first symptoms heralding disease progression. We have seen a patient whose symptoms were recognizable at age 2.5 years and several patients whose symptoms began in the 8th or 9th decade. Disease duration averages around 15-20 years, with much individual variation. Cerebral imaging by CT or MRI shows symmetric atrophy of the caudate nucleus, followed later by diffuse cortical atrophy. Caudate atrophy is often not discernable at the time of intiial diagnosis. PET scanning may detect metabolic changes before the advent of clinical symptoms (46).

About 5-10% of HD-affected individuals have symptom onset in the first two decades of life. About 90% of individuals with childhood onset HD have received their disease gene from an affected father. Symptoms in juvenile-onset patients are generally very different from the characteristic features of adult-onset HD. Chorea is much less common as a presenting feature than rigidity. Behavior and cognitive difficulties are usually recognized early, perhaps because of the highly scrutinized social and academic environments that most children live in. Generalized and/or myoclonic seizures are more common in childhood-onset than adult-onset HD, occurring in up to 30% of children.

Spinal and bulbar muscular atrophy (SBMA, Kennedy's disease)

SBMA is a neuromuscular disorder caused by CAG repeat expansions in the androgen receptor gene. It differs clinically from the other CAG repeat disorders in at least four immediately obvious ways: 1) it is an X-linked disorder; 2) full expression of the disease phenotype is restricted to males; 3) the primary neurologic

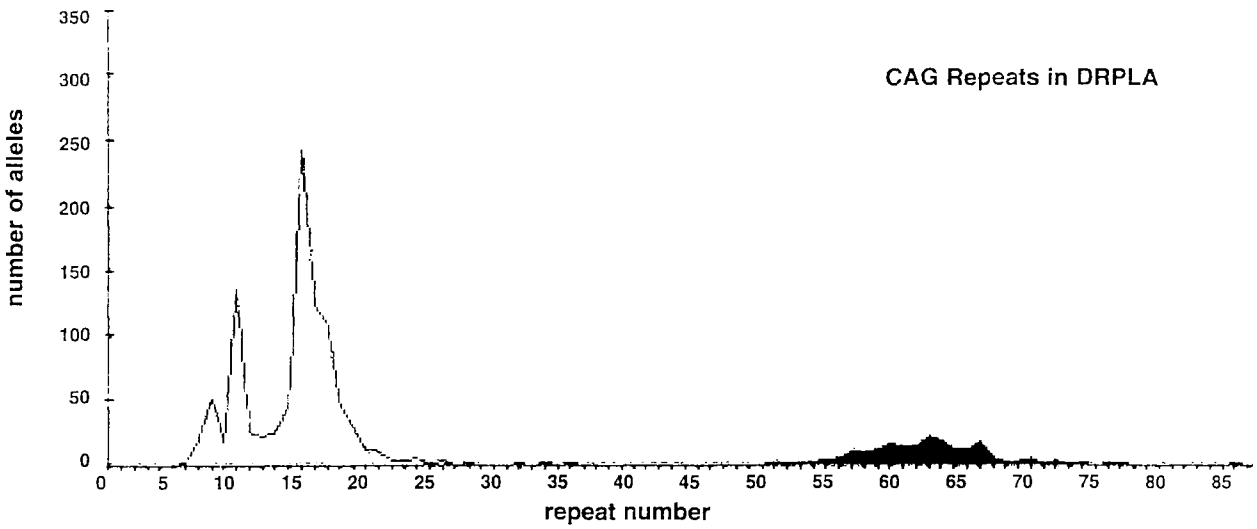

Figure 1. c. DRPLA (N= 925 normal alleles, 195 expanded alleles) (3, 4, 61, 73, 74, 83, 101, 109, 123, 124, 137, 138, 141, 163, 185)

effects are on anterior horn cells rather than central nervous system structures; and 4) the disease directly affects male endocrine function as well as neurologic function. Whereas CAG repeat expansions in the androgen receptor gene cause SBMA, point mutations, deletions, and other mutations, which would be expected to truncate the androgen receptor protein or to decrease function of the androgen receptor, do not cause SBMA, but do cause androgen resistance syndromes. These have been reviewed (48).

Kennedy, Alter, and Sung are generally recognized as the first to provide a detailed description of this condition (72), although other cases may have been reported earlier (76, 89, 95, 117, 165). The clinical and pathological features of the disease have been reviewed, but not since the discovery of disease-causing CAG expansions within the androgen recepotor gene (5, 156, 173). We review here more than 40 clinical reports describing about 250 patients from over 60 families, and about 50 reported sporadic cases, of ethnic backgrounds including American, Australian, and Eastern and Western European Caucasian (including Belgian, English, German, Greek, Italian, Polish, Spanish, Swiss, and Turkish); Chinese, Japanese, Korean, and Vietnamese; Chippewa; and French Canadian (1, 5, 6, 8, 10, 20, 25-27, 31, 33, 41, 52, 54, 58, 70, 72, 79, 80, 89, 91, 95, 97, 98, 102, 104, 111, 112, 116, 117, 120, 126, 132, 142, 143, 149, 150, 155-157, 160, 167, 168,173, 174, 179, 184). Prevalence data are not known for SBMA; one author suggests that it may represent about 2% of cases of "ALS" (151). Many cases have been reported in the Japanese literature (reviewed in 156), suggesting that the disease may either be more common or more commonly recognized in that country.

Disease onset has been reported as early as the teenage years (for androgen-insensitivity effects) and as late as the 8th decade, although symptoms most commonly begin in the 3rd to 5th decades of life. All affected individuals eventually develop an insidious neurogenic weakness with progressive atrophy of limb muscles and tongue. Impaired gait is often the first symptom of weakness, with changes in handwriting and speech representing other common presenting symptoms. Weakness is slowly progressive over years to decades, and is never accompanied by upper motor neuron signs (hyperreflexia or spasticity); hyporeflexia may be seen. Creatine phosphokinase (CPK) levels were elevated in 77% of patients, with levels generally in the range of 200-1200 IU.

However, limb weakness may not be the presenting symptom. In the reported cases reviewed here, four other symptoms were very common, and were seen to evolve in any order or combination: oral-lingual fasciculations with dysarthria and dysphagia (89%); tremor (82%); muscle cramps (65%); and gynecomastia (65%).

The oral-lingual fasciculations are very prominent and may resemble myokymia electrically but may increase with voluntary contraction of the involved muscles. They have been studied electrophysiologically (112). Neurogenic weakness of the bulbar muscles with resultant dysarthria and dysphagia accompany these unusual movements. A fine action or postural

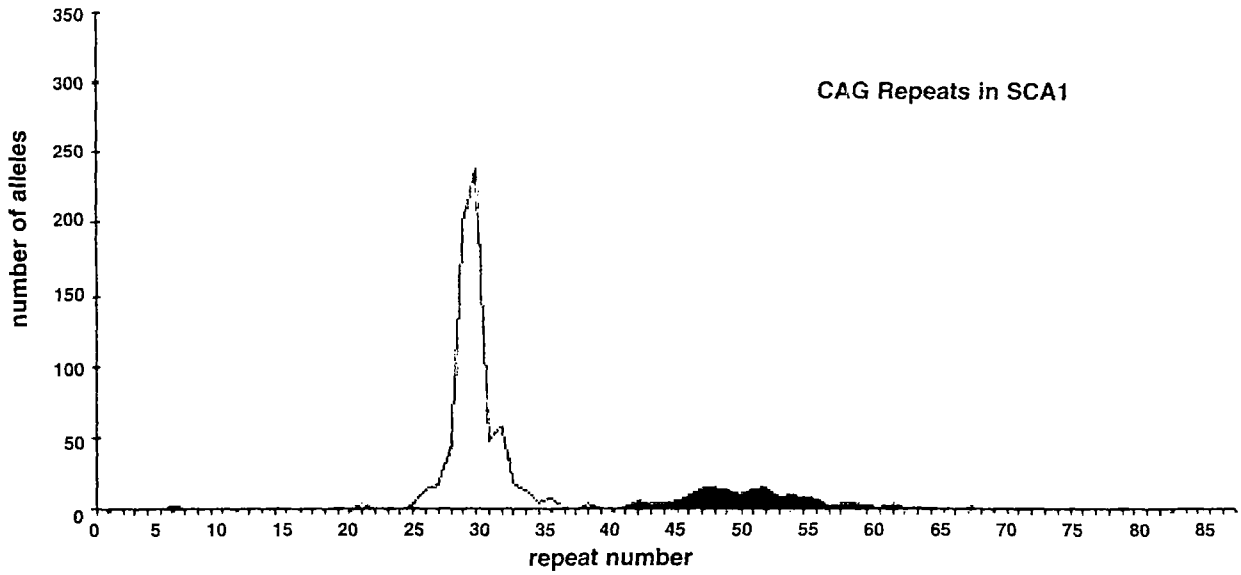

Figure 1. d. SCA1 (N=677 normal alleles, 163 expanded alleles) (21, 22, 28, 38, 45, 66, 69, 94, 115, 127, 128, 135, 152)

tremor is common and may precede any other motor symptoms of SBMA, causing the disease to masquerade as essential tremor (70). This tremor resembles the tremor seen occasionally in patients with neuropathy. Muscle cramps may precede by years or decades any other symptoms of SBMA; initially, they are often exercise- or cold-induced. In addition to muscle cramps, a small number of affected males have been reported to have episodes of increased weakness resembling myasthenia (31, 116, 160); EMG in one case showed a decremental response (31).

Finally, gynecomastia, a harbinger of testosterone-resistant endocrine dysfunction, is seen in somewhat more than half of males with SBMA. Although this is usually a later phenomenon, occasional patients have required surgical treatment of gynecomastia in their teens or twenties, before the onset of other symptoms. Gynecomastia is often accompanied by other evidence of endocrine dysfunction, including testicular atrophy, impotence, and low sperm counts (1, 5, 31, 41, 52, 54, 102, 142, 173); that these are later phenomena is demonstrated by the ability of most affected individuals to father children. Testosterone levels are usually normal but may be slightly low, and estrogen and FSH levels are commonly (but not always) elevated (143). Decreased androgen binding capacity (25, 89, 173) and decreased androgen receptors in scrotal skin (94) have been reported, although a later study suggests that androgen receptors are present in muscle fibers of affected patients (98). Although diabetes was reported in several early cases, it appears not to be an integral part of the disease.

Many studies have reported EMG, muscle biopsy (5, 6, 42, 52, 54, 91, 142, 143, 173, 174, 179), or autopsy findings in SBMA. The EMG consistently shows findings consistent with neurogenic muscle atrophy. Muscle biopsies likewise show group fiber loss, suggesting neurogenic atrophy, and loss of anterior horn cells is confirmed by autopsy (72, 102, 156, 157). Autopsies have generally confirmed the clinical impression that the forebrain is normal.

Muscle cramps have been occasionally described in female carriers of SBMA, generally without other symptoms (8, 10, 72, 120, 143, 155). A minority of carrier females have tremor, fasciculations, or muscle biopsy abnormalities, but a progressive degenerative course has never been reported.

Dentatorubropallidoluysian atrophy (DRPLA)

The name dentatorubropallidoluysian atrophy was first applied in 1958 to a group of patients with ataxia and a hyperkinetic movement disorder with characteristic neuropathologic findings (154), although the condition was probably first described in the 1940s (166, 170). Since that time, DRPLA has been recognized most frequently in Japan, where the prevalence has been estimated at about 0.4-0.7/100,000 (61,62). Clinical and pathologic features of the condition have been reviewed (59,175). The cardinal features of DRPLA include dementia, ataxia, chorea, myoclonus, and epilepsy. In Japan, two typical phenotypes are recognizable: Type 1, or adult-onset DRPLA (average onset age 44 years),

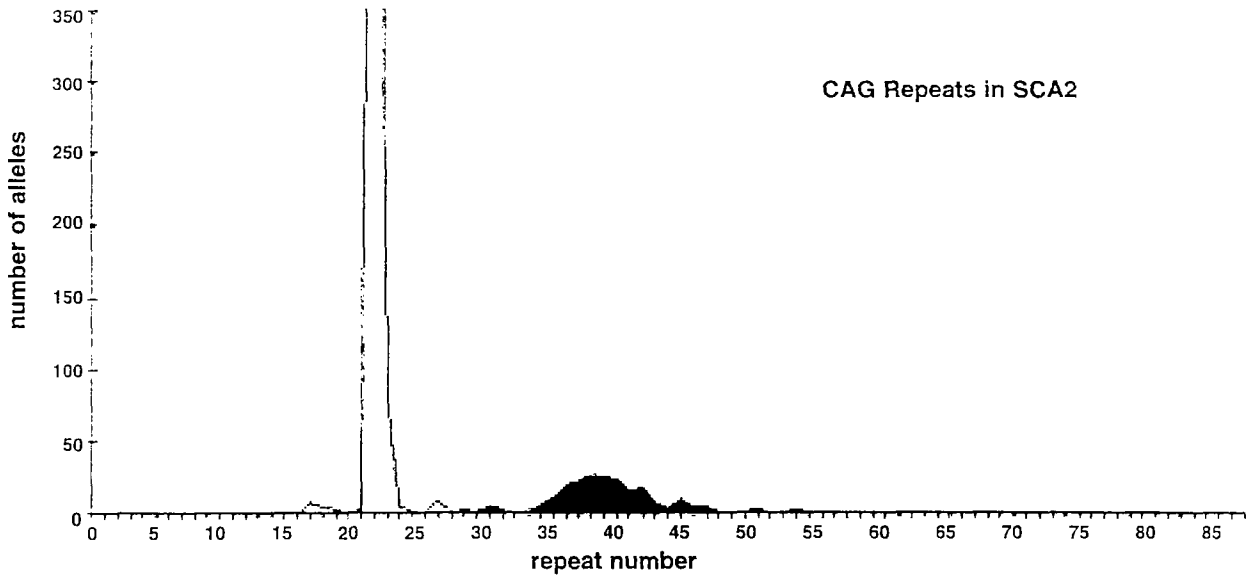

Figure 1. e. SCA2 (N= 1131 normal alleles, 208 expanded alleles) (39, 63, 125, 130, 139)

with a high incidence of ataxia, chorea, and dementia, and less often epilepsy and myoclonus, progressing over 10-20 years; and Type 2, or childhood-onset, DRPLA, a more rapidly progressive condition with prominent myoclonus, epilepsy, learning disabilities/mental retardation, and relatively less chorea and ataxia (74). About 45% of patients have early onset, Type 2, DRPLA, most of whom have affected fathers (74). Several recent authors have stressed the prominence of psychiatric symptoms early in the disease (123, 124, 177). When DRPLA has been recognized in individuals of European descent, it has usually been (mis)diagnosed previously as Huntington disease (23, 123, 176, 177). Neuroimaging has been reported in a very small number of cases, but should easily distinguish DRPLA from HD because of the prominent cerebellar atrophy which accompanies diffuse cortical and brainstem atrophy in DRPLA. Neuropathologic analysis confirms that the dentate nucleus and globus pallidus are the primary sites of neuronal cell loss, with prominent secondary atrophy of the outflow tracts from those structures (59,101,154,162,175,177).

An allelic condition was described in a large African-American kindred (16,32), known as the Haw River syndrome. Clinical features of this condition include ataxia, chorea, dementia, and seizures, along with mental retardation and/or psychiatric disturbance. It is distinguished from DRPLA by the additional radiologic and pathologic findings of marked demyelination of the centrum semiovale and atrophy of the dorsal columns in the spinal cord. Degeneration of the posterior columns was noted in one additional DRPLA family (119).

The spinocerebellar ataxias

The epidemiology of the spinocerebellar degenerations has been studied, but using non-molecular definitions of the diseases. The prevalence of all spinocerebellar degenerations in Japan was estimated to be 4.53/100,000 (57). The prevalence of hereditary ataxias has been estimated to be 3.5-8.5/100,000 in several European series (12,35,82,122), and 27/100,000 in Libya (159).The most satisfactory clinical classification scheme for the ataxias in the pre-molecular era was that of Harding (50,51), who used the terms "autosomal dominant cerebellar ataxia Type 1" (ADCA I) for ataxias with neurologically complex phenotypes but without retinal degeneration, ADCA II for ataxias with retinal degeneration, and ADCA III for pure cerebellar ataxia. Seven different SCA genes have been localized, of which four, SCA 1, SCA 2, SCA 3, and SCA 6 have been identified. SCA1, SCA2, and SCA 3 are forms of ADCA I, and are discussed in detail below. SCA 4 is another form of ADCA 1 (36), while SCA 5 appears to represent a form of ADCA III (129), and SCA 7 is a form of ADCA II (2, 9a). Very little clinical information is available about SCA 6, but it appears to represent a type of pure cerebellar ataxia, or ADCA III. Molecular epidemiologic data suggest that SCA1, SCA2, and SCA3 combined are responsible for 50-75% of ADCA I (19, 30,128,144,152). In most populations studied,

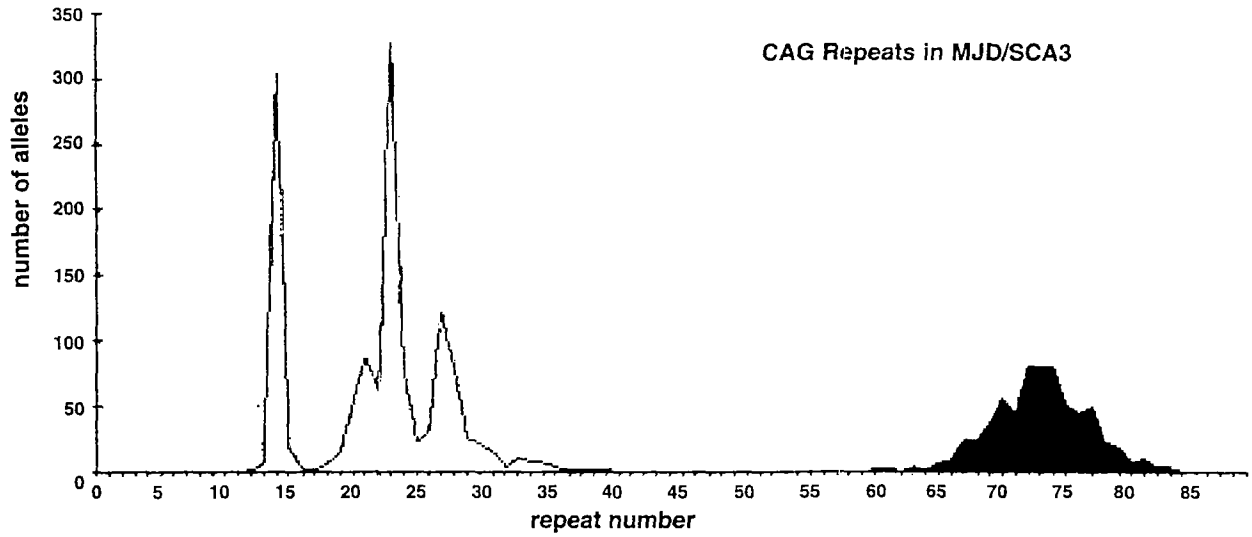

Figure 1. f. SCA3 (N= 1322 normal alleles, 663 expanded alleles) (18, 30, 58, 65, 71, 84, 88, 93, 128, 135 161, 164)

SCA 3 is the most common of the three types of ataxia, and SCA1 is the least common, with one study of British and Italian families representing a notable exception (42). Population isolates with a high incidence of SCA2 (114, 40) and SCA1 (44, 45, 69) due to a founder effect have been identified. Sporadic ataxia is rarely if ever caused by mutations in the SCA1, SCA2, or SCA3 genes (128, 131, 152).

Cerebral imaging in the ataxias has been reported, largely prior to the advent of molecular genetic diagnostic methods (121, 133, 180, 182). Four distinct patterns of imaging abnormalities can be seen: atrophy of the cervical spinal cord, always observed in Friedreich's ataxia, but less often found in patients with dominant or idiopathic cerebellar ataxia; atrophy of the cerebellar hemispheres and vermis alone or far out of proportion to any brainstem atrophy, seen in the pure cerebellar degenerations; atrophy of the pons, cerebellum, middle cerebellar peduncles, and medulla, which is the pattern seen in sporadic olivopontocerebellar atrophy and some of the dominant ataxias; and mild nonspecific diffuse infratentorial atrophy. A recent study suggests that SCA2 can be distinguished from SCA3 radiologically, with SCA2 showing severe olivopontocerebellar atrophy and SCA3 showing only mild cerebellar atrophy without severe pontine or medullary loss (15). According to these authors, SCA1 occupies an intermediate position radiologically, with atrophy of the pons and medulla being evident but less pronounced than in SCA2.

Spinocerebellar ataxia type 1 (SCA1). SCA1 was described in 1941 in a family which was later studied in great clinical detail by two neurologists who were themselves members of the kindred (47, 49, 145-148). A number of additional families of varied ethnic backgrounds (Caucasian, African-American, Japanese, Siberian) have since been described (24, 28, 38, 44, 45, 108, 140, 158, 183, 188). Molecular genotype data suggest that SCA1 is less common than SCA2 or SCA3 as a cause of adult-onset autosomal dominant ataxia; published series suggest that 6-15% of index cases have SCA1 (39, 127, 152). The earliest clinical symptoms of SCA1 include imbalance, slurred speech, and changes in handwriting. Early clinical findings include slowness in initiating and reacting to movements, slow or infrequent eye-blinking, and abnormal eye movements, including hypermetric saccades, lateral gaze-evoked nystagmus, and saccadic intrusions in pursuit eye movements. The saccades later become slowed, giving way to frank ophthalmoplegia late in the course. Affected individuals develop a pan-cerebellar ataxia, with limb, ocular, gait, and truncal ataxia, and dysarthria. In addition to ataxia, affected individuals often develop signs of involvement of other neurologic systems, such as the pyramidal tracts (hyperreflexia, extensor plantar responses, and clonus), or less commonly, extrapyramidal signs (involuntary movements or bradykinesia), in varying combinations and to varying degrees. Bulbar involvement is prominent as the disease progresses, leading to severe dysarthria and dysphagia, with tongue fasciculations and impaired cough reflex evident on

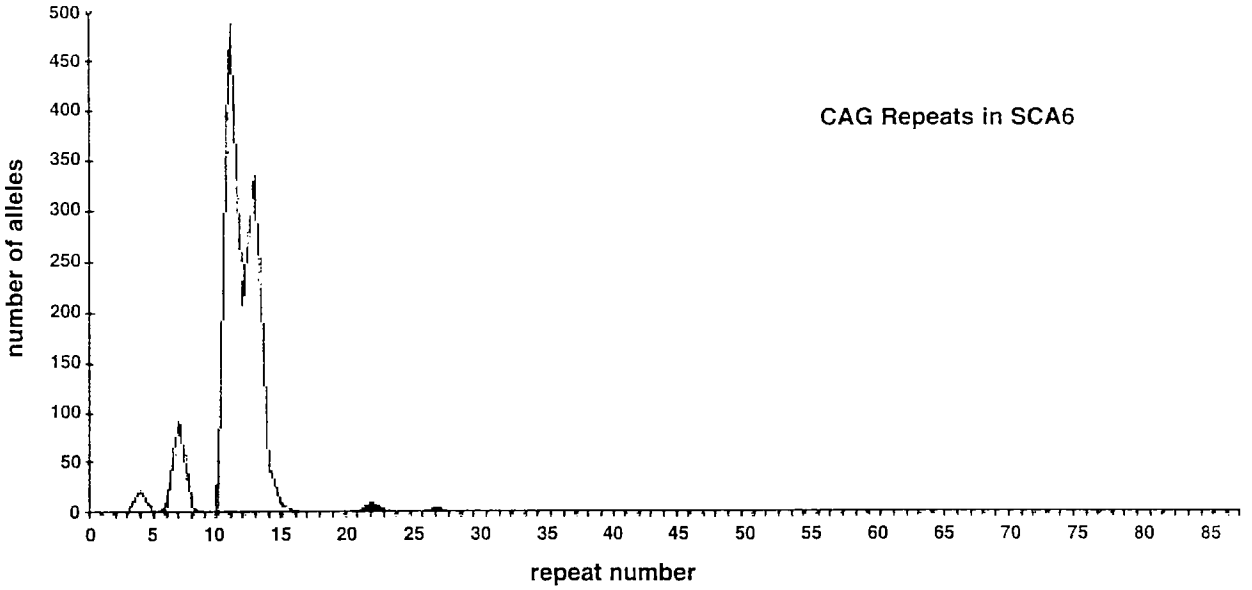

Figure 1. g. SCA6 (N= 1208 normal alleles, 18 expanded alleles) (187)

examination. Choking and its consequences (aspiration pneumonia and poor nutrition) are common causes of death. Dementia and symptomatic neuropathy or amyotrophy are late findings. The average age of onset in the Schut kindred was 26 years (range 17-35 years), with an average disease duration of 11.6 (female)-14.4 (male) years, and an average age of death of 37 years (49). A recent review of Japanese SCA1 kindreds yielded somewhat different results, with a mean onset age of 36 years (range 15-63), and a disease duration of 21 years (140). Within- and among-kindred variability in disease onset age and duration has been reported for other kindreds (24, 188).

Spinocerebellar ataxia type 2 (SCA2). SCA2 was not recognized as a separate entity until genetic linkage studies in 1993 showed a large Cuban kindred with ataxia similar in phenotype to SCA1 but not linked to the SCA1 locus (40, 114), although it may have been described first in 1971 (172). The SCA2 locus was mapped to chromosome 12q, and several additional kindreds were quickly found to localize to the same region (7, 29, 34, 85, 125). Clinically, individuals with SCA2 develop ataxia of gait and limb, with several authors emphasizing the additional early presence of slowed saccadic eye movements (ophthalmoparesis), as well as evidence of peripheral nerve dysfunction (depressed tendon reflexes, fasciculations, action/postural tremor, and/or muscle cramps). Spasticity, parkinsonism, optic atrophy, and retinal degeneration are not seen. Prominent dementia and chorea were noted in patients with higher CAG repeat numbers and a younger age of onset (29, 39). Onset age under 20 years is reported more commonly in SCA2 than in SCA1 or SCA3. While most of the initial SCA2 work described single large kindreds with multiple affected individuals, a recent study reviewed the clinical features of SCA2 in a more diverse population of autosomal dominant ataxia type I patients from an ataxia clinic (39). These authors commented on the striking variability in clinical symptomatology between different families (who were also of different ethnic backgrounds), and suggested that genetic background may have an important effect on the phenotypic expression of the disease gene. One recent study suggests that careful oculographic and radiologic studies can reliably distinguish SCA2 from SCA1 and SCA3 (15).

Spinocerebellar ataxia type 3/Machado-Joseph disease (SCA3/MJD). SCA3/MJD is the most clinically heterogeneous of the hereditary ataxias, with symptoms ranging from a pure Parkinsonian syndrome to a spastic ataxia. SCA3 was first described in 1972 in two American families of Portugese (Azorean) descent (105, 181). Rosenberg promoted the name "Machado-Joseph disease", the surnames of the first two known large Portugese kindreds, for this disease, which was felt for many years to be restricted to individuals of Portugese origin (134). Some authors thus defined a condition distinct from the original Portuguese families, with a more restricted, ataxia-dominant phenotype, and differentiated it from MJD, labelling it SCA3 (56, 67). However,

Disease	Epidemiology	Primary symptoms	Age of onset	Location of primary Neuropathology
HD	3 - 7 / 100,000 Caucasian; < 1 / 100,000 Asian; new mutations about 1 - 3% of cases	chorea, dementia, psychiatric disturbance, weight loss	age 35 - 40 (range 2 - 80s)	caudate nucleus
DRPLA	0.4 - 0.7 / 100,000 in Japan	ataxia, dementia, seizures, chorea, myoclonus	Type 1 age 44 (up to 7th decade) Type 2 age 8 (up to 20 by definition)	dentate nucleus, globus pallidus and outflow tracts
SCA1	unknown; responsible for about 10 - 27% of dominant ataxia	ataxia, bulbar dysfunction, variable pyramidal tract, peripheral neuropathy	3rd - 4th decade (range <10 to >60)	cerebellar, brainstem nuclei, spinocerebellar tracts
SCA2	unknown; responsible for 13 - 24% of dominant ataxia	ataxia, opthalmoplegia, neuropathy, chorea, dementia	3rd - 4th decade (range 2 - 60s)	cerebellar, brainstem nuclei
SCA3	unknown; responsible for 11 - 36% of dominant ataxia	ataxia, impaired upgaze; spasticity, rigidity, dystonia, Parkinsonism; neuropathy, amyotrophy, weakness; oral and facial fasciculations	35 - 40 (range 10 - >70)	dentate, brainstem nuclei; anterior horn cells, dorsal root, spinocerebellar tracts
SCA6	unknown; described in four families	ataxia, abnormal eye movements, mild sensory loss	age 26 - 50s	dentate and olivary nuclei
SBMA	unknown; present in many ethnic groups	limb and bulbar weakness, gynecomastia	20-50 (range teens to 70s)	anterior horn cells

Table 1. Clinical features of CAG repeat disorders

many kindreds of diverse ethnic backgrounds have been described since, particularly since molecular diagnosis became available (30, 42, 88, 92, 93). It is now clear that SCA3 and MJD are caused by the same genetic mutations and simply reflect the phenotypic variability of this disease.

Clinically, three SCA3 phenotypes are common. In younger patients with Type 1 SCA3, prominent pyramidal (spasticity, hyperreflexia) and/or extrapyramidal (rigidity, dystonia, involuntary movements) signs may exceed or accompany ataxia and ophthalmoplegia as the most striking symptoms. Type 2 SCA3 presents in early to mid-adulthood, usually with ataxia and pyramidal or extrapyramidal (dystonia) signs. Patients presenting with SCA3 after age 40 (Type 3) generally do not have spasticity or Parkinsonism accompanying ataxia and ophthalmoparesis, but may instead have prominent peripheral signs of neuropathy or anterior horn cell loss, with amyotrophy, fasciculations, and weakness. A fourth presentation which appears to be much less frequent is an ataxia-less presentation, in which individuals have Parkinsonism (tremor, rigidity, gait disturbance) and neuropathy (17, 42). Oral-facial fasciculations are common, and "bulging eyes" are often described. The clinical presentation appears to "run true" in some large families (when the large Joseph family was first studied, for instance, cerebellar symptoms were not seen in any affected individuals [134]).

Phenotypical overlap for the inherited ataxias appears to be the rule. Even experienced clinicians cannot reliably distinguish SCA1 from SCA3 on the basis of purely clinical symptoms (30, 42), as any particular patient with either disease may have ataxia alone or in combination with any of the additional symptoms noted above.

Spinocerebellar ataxia type 6 (SCA6). At the time of this writing, spinocerebellar ataxia 6 (SCA6) is the newest member of the CAG repeat disorder group. Zhuchenko et al. reported four families with CAG repeat expansions in the gene on chromosome 19p13 which encodes the α-1A-voltage-dependent calcium channel (CACNL1A) (187). SCA6 is allelic with two other neurologic disorders, episodic ataxia type 2, and familial hemiplegic migraine. Missense and other protein-truncating mutations in the CACNL1A gene result

Disease	Inheritance	Gene discovered	Chromosomal location of gene	Gene name	Protein name	Number of affected individuals studied molecularly
Huntington Disease	AD	1993	4p1.6	IT15	huntingtin	> 2,500
DRPLA	AD	1994	12p13	CTG-B37	atrophin-1	about 200
SCA1	AD	1993	6p22 - 23	SCA1	ataxin-1	about 160
SCA2	AD	1996	12q23 - 24.1	SCA2	ataxin-2	about 200
SCA3	AD	1994	14q32.1	SCA3	ataxin-3	660
SCA6	AD	1997	19p13	SCA6	α1A-voltage-dependent calcium channel	18
SBMA	XL	1991	Xq13 - 21	SBMA	androgen receptor	about 250

Table 2. Genetic features of CAG Repeat Disorders
*AD= autosomal dominant; XL= X-linked

in one of these two other disorders, whereas expansions of a CAG repeat sequence are associated with SCA6 (113, 187).

The four families with SCA6 were identified by screening a panel of 133 index cases with ataxia for expansions of the CAG repeat sequence which was known to be located in the CACNL1A gene. Eight index cases were identified (6% of the sample), but only four were available for further study. The disorder is dominantly inherited; its frequency and other epidemiologic characteristics are unknown. Clinical information is available for a total of twenty affected individuals from the four families. The clinical features of the disease include mild and slowly progressive ataxia of limbs and gait, dysarthria, prominent and early nystagmus, and mild vibratory and proprioceptive sensory loss later in the disease. Prominent early loss of optokinetic nystagmus and mild hyperreflexia were present in one family (Dobyns, personal communication). In three of four families, symptoms began in the 5th-6th decade, and progressed over 20-30 years before affected individuals became wheelchair-bound. Some older patients developed bulbar symptoms with choking. In one family, symptoms began earlier (26-31 years), but were still very slowly progressive. Cerebral imaging has shown cerebellar atrophy only, without cortical, brainstem, or upper spinal cord atrophy. Pathologic features include severe loss of Purkinje cells, with moderate loss of granule cells and neurons in the dentate nucleus, and mild to moderate loss of neurons in the inferior olive.

MOLECULAR GENETIC ANALYSIS OF THE CAG REPEAT DISEASES

The common thread joining the seven neurodegenerative diseases described above is their single distinctive type of genetic mutation, which is expansion of a CAG repeat sequence within the coding region of the gene. What is known of the mechanisms by which CAG repeat expansions cause disease will be reviewed elsewhere in this volume; here, we will describe the clinical-genetic features that have been explained by the discovery of this novel type of mutation and point out similarities and differences among the known CAG repeat disorders.

Inheritance patterns and gene products

All but one of these disorders have autosomal dominant inheritance patterns; this and other basic information about the genes and diseases are shown in Table 2. Autosomal dominant inheritance, of course, implies that 50% of the offspring of affected individuals should inherit the disease gene. Two recent studies, however, found a higher incidence of affected offspring among individuals with DRPLA , SCA1, and SCA3, suggesting that "meiotic drive" may exist for the mutant alleles for these diseases (60, 130). In addition, another recent study demonstrated increased genetic fitness among carriers of mildly expanded SCA1 and HD alleles, suggesting another mechanism by which genes with expanded CAG repeats can be maintained in the population (37). Although homozygotes for the expanded HD and SCA1 genes appear to fare no differently than heterozygotes in terms of disease onset, course, or severity, homozygotes

Disease	Normal CAG repeat range	Abnormal CAG repeat range	Correlation (r) between repeat number and onset age	Meiotic instability of expanded alleles	Somatic instability reported	New mutations reported	Reduced penetrance reported*
HD	9 - 35	36 - 121	-0.5 to -0.89	male 69%; up to +74 female 32%; up to +16	yes	1 - 3%	yes
DRPLA	3 - 36	52 - 88	-0.69 to -0.84	male 92%; +1 to +28 female 94%; -4 to +5	yes	yes	yes
SCA1	6 - 39	39 - 81	-0.74 to -0.81	male 77%; -4 to +28 female 59%; -6 to +4	yes	no	yes**
SCA2	15 - 34	34 - 64	-0.77 to -0.86	male 78%; -7 to +24 female 86%; -1 to +15	not studied	1 sporadic case	no
SCA3	12 - 40	61 - 84	-0.43 to -0.92	male 75%; -5 to +9 female 75%; -8 to +3	yes	2 sporadic cases	no
SCA6	4 - 16	21 - 27	not studied	not reported	not studied	no	no
SBMA	9 - 33	38 - 75	-0.59 to -0.801	male 77%; -2 to +5 female 24%; -4 to +2	no	common? (up to 20%)	no

Table 3. Clinical genetics of CAG repeat disorders
*reduced penetrance refers to the existence of asymptomatic individuals over age 70 years with repeat lengths that have been associated with the presence of disease symptoms inother individuals.
**a single 66-year old individual with 44 repeats from a large kindred in which the oldest known onset age is 56 years (45)

for the SCA3 and DRPLA genes may have an earlier symptom onset (77, 78, 141). Of interest, CAG expansions in the AR gene appear to function in a sex-limited fashion, as female carriers of these expansions may develop muscle cramps, while hemizygous males develop a progressive, neurodegenerative disorder.

The normal roles of the proteins encoded by the CAG repeat disorder genes are known only for the androgen receptor gene in SBMA and the α1A calcium channel in SCA6. The normal functions of ataxins 1-3, huntingtin, and the protein encoded by the DRPLA gene are not known. The CAG repeat expansions in all of these genes are expected to result in elongated polyglutamine tracts within the encoded protein (discussed further elsewhere in this volume). The number of patients who have been studied molecularly remains rather small for all of these diseases, so cautious interpretation of the clinical-molecular correlations remains appropriate.

Distribution of normal and abnormal CAG repeat numbers

In Table 3, clinically important molecular data are summarized. Subtle differences among the normal and abnormal CAG repeat ranges and distributions for the different diseases are evident (Figure 1). For instance, while the distribution of normal repeat numbers for the HD gene and the androgen receptor gene is rather broad, only a few CAG repeat lengths for the SCA1 and SCA2 genes are seen with any frequency in the normal populations studied. This is probably related to interruptions within the CAG repeat sequences of those two genes (CAT for SCA1 and CAA for SCA2), which appear to confer stability on the repeat sequence. For DRPLA and SCA3, several discrete allele sizes are seen at a high frequency in the normal population, rather than the broad distribution found in HD and SBMA. The gaps between normal and disease allele sizes are also notably different among the different disorders (Figure 1), suggesting that different mechanisms of mutagenesis and disease pathogenesis may be operating in the different disorders.

Several authors have commented that the distribution of normal allele sizes for various CAG repeat genes varies among different ethnic groups (64, 84, 135); these differences are intriguing, and may underly the variable frequencies of particular CAG repeat disorders in different populations.

Instability of expanded CAG repeats and new mutations

All studies of all CAG repeat diseases have shown a significant and clinically important negative correlation between age of disease onset and repeat number, indicating that the size of the repeat expansion is a major determinant of disease onset age. Likewise, with the

exception of SCA6 (for which a very small sample has been examined), all studies of parent-child pairs and of single sperm have shown that expanded CAG repeat sequences are unstable in meiosis, particularly male meiosis (Table 2), in comparison with normal alleles, which are stably transmitted (18, 21, 79, 81, 87). While further lengthening of an expanded allele is the most common change, ample reports of intergenerational decreases in CAG repeat length and stably transmitted alleles exist. Both the frequency and the magnitude of CAG repeat instability may depend on the sex of the parent and the disease gene under study (Table 2), with less instability evident among women transmitting expanded CAG repeats in the androgen receptor gene, compared with up to 92% of DRPLA disease alleles showing instability (61, 73, 74, 109, 123, 124, 141). The molecular mechanisms underlying meiotic instability and the relationship betweeen disease onset and CAG repeat size are not fully understood; what is known and speculated will be discussed in this volume by La Spada.

New mutations for CAG repeat disorders can occur by expansion of alleles which themselves are not able to cause the disease but which are meiotically unstable. *De novo* expansion of a CAG repeat from a non-disease causing size to the disease-causing range has been proven for a small number of individuals with HD (43, 99). Several "sporadic" cases of DRPLA have been reported (61, 73), at least one with parents who were documented to have no neurologic disease at the time of their deaths in their 80s. One DRPLA-affected individual homozygous for 57 CAG repeats was reported (141). Both parents had 57 CAG repeats and were asymptomatic at age 72 and 74 years. Thus, two abnormal alleles were transmitted stably to form a homozygous affected offspring by parents who did not have a disease phenotype. The finding that mutations in the SCA1, SCA2, or SCA3 genes are very uncommon among patients with "sporadic" ataxia suggests that new mutations in these genes are rare (128, 131, 152). Parental genotypes of the rare sporadic SCA2 and SCA3 cases have not been reported. New mutations for SBMA are postulated by pedigree analysis, showing fairly frequent sporadic cases of the disease, but have not been proven molecularly.

Mild somatic instability for CAG repeat number has been documented for HD, SCA 1, SCA3, and DRPLA (4, 21, 163, 169), and is discussed elsewhere in this volume. In one study of a patient with SBMA, somatic mosaicism for CAG repeat number was not observed in multiple nervous system and non-nervous system tissues examined (165), and a study of fetal tissues containing an expanded CAG repeat within the huntingtin gene showed no variability among the non-nervous system tissues studied (9). The clinical relevance of somatic tissue mosaicism for CAG repeat number has not been determined.

Nonpenetrance, mutability, and "intermediate alleles"

The existence of *de novo* mutations suggests that some CAG repeat sequences acquire the (presumably) abnormal property of meiotic instability before acquiring the ability to cause disease. That the ability to cause disease in these "dynamic mutation" disorders is not an all-or-none phenomenon has been supported by the observation of incomplete penetrance of disease phenotypes for repeat lengths at the low end of the abnormal range. Nonpenetrance of IT-15 gene CAG expansions in the range of 36-39 repeats has been reported (13, 136, reviewed in 106; US HD Genetic Testing Group, in preparation). Apparent nonpenetrance (or very late onset age) has been observed also for DRPLA (77, 141), SCA1 (45), and SCA2 (131). The last authors also observed SCA2 alleles in patients with sporadic ataxia which were larger than any reported alleles in normal individuals (32 and 34 CAG repeats, as well as several patients with 30 or 31 repeats), but were reluctant to call these allele sizes abnormal, as they are smaller than any previously reported affected alleles. We have included those as abnormal alleles in Figure 1D, but have abided with the authors' conservative interpretation of the normal and abnormal ranges in Table 3 (Pulst, personal communication). Alleles of intermediate size or incomplete penetrance have not been reported for SCA3 or SBMA. Because of the strong correlation between onset age and repeat number, proof of nonpenetrance technically requires that very elderly individuals carrying expanded CAG repeats are clinically and pathologically normal. More practically, nonpenetrance has been defined in terms of individuals living beyond expected normal lifespans without clinical or pathological signs of disease.

The terms "intermediate" or "indeterminate" have been applied to IT-15 alleles which are in the border zone between normal and abnormal CAG repeat lengths. Recent work has shown that these terms encompass two different entities: alleles of a size which do not cause HD, but from which *de novo* mutations have occurred; and alleles which can cause HD but which are not fully penetrant. As experience has allowed these two entities to be distinguished, we prefer the more specific descriptors "mutable" and "reduced penetrance", respectively, to describe allele sizes in these ranges. Mutable alleles do not themselves cause disease symptoms (i.e. are normal), but can give rise to *de novo* mutations, probably due to meiotic instability combined with proximity to the disease threshold. Alleles in the range of 27-35 repeats have been reported in the parents of *de novo* mutation carriers, and should

thus be considered mutable. "Reduced penetrance" should be used to describe alleles which can cause disease symptoms but do not always do so within a normal life expectancy. The range in which reduced penetrance for HD has been reported is 36-39 CAG repeats (136). Empiric mutability or penetrance risks for specific repeat lengths between 27-39 CAG repeats are not yet available. For the other diseases such as DRPLA, SCA1, and SCA2, alleles intermediate in size or behavior between the normal and abnormal ranges may exist; insufficient data are available to categorize these alleles, and the nonspecific terms "intermediate" or "indeterminate" may be used.

Summary

In the last six years, seven neurodegenerative diseases have been found to be caused by expansions of intragenic CAG repeat sequences. The diseases share a variable (usually adult) age of onset, which is highly dependent on the length of the CAG repeat, and effects on multiple systems within the central and peripheral nervous systems. The cerebral cortex is not a primary site of pathology for any of the diseases, and organs other than the nervous system are not primarily affected (except for SBMA). The diseases differ in their primary site of neuropathology, and for that reason have widely varying neurologic profiles. The distributions of normal and abnormal CAG repeat sizes vary among the diseases, and suggest that different mechanisms of mutagenesis or disease pathogenesis could exist for the different disorders.

The dynamic nature of trinucleotide repeat mutations has clarified a number of clinical and genetic observations in these diseases. New mutations arising from mutable normal alleles have been reported for some of the diseases. The tendency to further expansion of an expanded allele provides a molecular correlate to the clinical observation of anticipation (171). Sex- and disease-dependent meiotic instability correlates with the observation of a paternal bias among juvenile onset cases for HD, SCA1 and DRPLA. Finally, reduced penetrance for alleles at the low end of the abnormal range has been observed for some (but not all) diseases in the group. Detection of CAG repeat expansions is relatively easy and inexpensive in the clinical laboratory, and molecular diagnosis has greatly improved diagnostic accuracy for this group of disorders. However, a full understanding of the biology and pathophysiology of this new class of mutations is still to come, and is awaited eagerly by clinicians and patients alike.

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