451e Classification of the Spinocerebellar Ataxias

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Ataxias with autosomal dominant, autosomal recessive, X-linked, or mitochondrial forms of inheritance are present on a worldwide basis. Machado-Joseph disease (SCA3) (autosomal dominant) and Friedreich's ataxia (autosomal recessive) are the most common types in most populations. Mutation markers are now commercially available to identify carriers at risk in their families, which allows for precise identification of the genetic mutation for correct diagnosis and also for family planning. Identification of positive mutation carriers with family planning has allowed for early detection of asymptomatic preclinical disease to reduce or eliminate the inherited form of ataxia in specific families on a global, worldwide basis.

TABLE 451e-1 CLASSIFICATION OF THE SPINOCEREBELLAR ATAXIAS (SCA)

Name	Locus	Phenotype
SCA1 (autosomal dominant type 1)	6p22-p23 with CAG repeats (exonic); leucine-rich acidic nuclear protein (LANP), region-specific interaction protein Ataxin-1	Ataxia with ophthalmoparesis, pyramidal and extrapyramidal findings; genetic testing is available; 6% of all autosomal dominant (AD) cerebellar ataxia
SCA2 (autosomal dominant type 2)	12q23-q24.1 with CAG repeats (exonic) Ataxin-2	Ataxia with slow saccades and minimal pyramidal and extrapyramidal findings; genetic testing available; 13% of all AD cerebellar ataxia
Machado-Joseph disease/ SCA3 (autosomal dominant type 3)	14q24.3-q32 with CAG repeats (exonic); codes for ubiquitin protease (inactive with polyglutamine expansion); altered turnover of cellular proteins due to proteosome dysfunction MJD–ataxin-3	Ataxia with ophthalmoparesis and variable pyramidal, extrapyramidal, and amyotrophic signs; dementia (mild); 23% of all AD cerebellar ataxia; genetic testing available
SCA4 (autosomal dominant type 4)	16q22.1-ter; pleckstrin homology domain-containing protein, family G, member 4 (PLEKHG4; puratrophin-1: Purkinje cell atrophy associated protein-1, including spectrin repeat and the guanine-nucleotide exchange factor, GEF for Rho GTPases)	Ataxia with normal eye movements, sensory axonal neuropathy, and pyramidal signs; genetic testing available
SCA5 (autosomal dominant type 5)	11p12-q12; β-III spectrin mutations; (SPTBN2); stabilizes glutamate transporter EAAT4; descendants of President Abraham Lincoln	Ataxia and dysarthria; genetic testing available
SCA6 (autosomal dominant type 6)	19p13.2 with CAG repeats in α_{1A}-voltage–dependent calcium channel gene (exonic); CACNA1A protein, P/Q type calcium channel subunit	Ataxia and dysarthria, nystagmus, mild proprioceptive sensory loss; genetic testing available
SCA7 (autosomal dominant type 7)	3p14.1-p21.1 with CAG repeats (exonic); ataxin-7; subunit of GCN5, histone acetyltransferase-containing complexes; ataxin-7 binding protein; Cbl-associated protein (CAP; SH3D5)	Ophthalmoparesis, visual loss, ataxia, dysarthria, extensor plantar response, pigmentary retinal degeneration; genetic testing available
SCA8 (autosomal dominant type 8)	13q21 with CTG repeats; noncoding; 3′ untranslated region of transcribed RNA; KLHL1AS	Gait ataxia, dysarthria, nystagmus, leg spasticity, and reduced vibratory sensation; genetic testing available
SCA10 (autosomal dominant type 10)	22q13; pentanucleotide repeat ATTCT repeat; noncoding, intron 9	Gait ataxia, dysarthria, nystagmus; partial complex and generalized motor seizures; polyneuropathy; genetic testing available
SCA11 (autosomal dominant type 11)	15q14-q21.3 by linkage	Slowly progressive gait and extremity ataxia, dysarthria, vertical nystagmus, hyperreflexia
SCA12 (autosomal dominant type 12)	5q31-q33 by linkage; CAG repeat; protein phosphatase 2A, regulatory subunit B, (PPP2R2B); protein PP2A, serine/threonine phosphatase	Tremor, decreased movement, increased reflexes, dystonia, ataxia, dysautonomia, dementia, dysarthria; genetic testing available
SCA13 (autosomal dominant type 13)	19q13.3-q14.4; potassium channel voltage-gated; KCNC3	Ataxia, legs > arms; dysarthria, horizontal nystagmus; delayed motor development; mental developmental delay; tendon reflexes increased; MRI: cerebellar and pontine atrophy; genetic testing available
SCA14 (autosomal dominant type 14)	19q-13.4; protein kinase Cγ (PRKCG), missense mutations including in-frame deletion and a splice site mutation among others; serine/threonine kinase	Gait ataxia; leg > arm ataxia; dysarthria; pure ataxia with later onset; myoclonus; tremor of head and extremities; increased deep tendon reflexes at ankles; occasional dystonia and sensory neuropathy; genetic testing available
SCA15 (autosomal dominant type 15)	3p24.2-3pter; inositol 1,4,5- triphosphate receptor type 1 (ITPRI)	Gait and extremity ataxia, dysarthria; nystagmus; MRI: superior vermis atrophy; sparing of hemispheres and tonsils
SCA16 (autosomal dominant type 16)	8q22.1-24.1	Pure cerebellar ataxia and head tremor, gait ataxia, and dysarthria; horizontal gaze–evoked nystagmus; MRI: cerebellar atrophy; no brainstem changes
SCA17 (autosomal dominant type 17)	6q27; CAG expansion in the TATA-binding protein (*TBP*) gene	Gait ataxia, dementia, parkinsonism, dystonia, chorea, seizures; hyperreflexia; dysarthria and dysphagia; MRI shows cerebral and cerebellar atrophy; genetic testing available
SCA18 (autosomal dominant type 18)	7q22-q32	Ataxia; motor/sensory neuropathy; head tremor; dysarthria; extensor plantar responses in some patients; sensory axonal neuropathy; EMG denervation; MRI: cerebellar atrophy
SCA19 (autosomal dominant type 19)	1p21-q21; KCND3; missense mutations; T352P; M373I; S390N; allelic with SCA22; overlaps with the locus of SCA22	Ataxia, tremor, cognitive impairment, myoclonus; MRI: atrophy of cerebellum
SCA20 (autosomal dominant)	11p13-q11; 260 kb duplication	Dysarthria; gait ataxia; ocular gaze–evoked saccades; palatal tremor; dentate calcification on CT; MRI: cerebral atrophy

(*Continued*)