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Review

Spinocerebellar ataxia: relationship between phenotype and genotype – a review

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Spinocerebellar ataxia (SCA) comprises a large group of heterogeneous neurodegenerative disorders inherited in an autosomal dominant fashion. It is characterized by progressive cerebellar ataxia with oculomotor dysfunction, dysarthria, pyramidal signs, extrapyramidal signs, pigmentary retinopathy, peripheral neuropathy, cognitive impairment and other symptoms. It is classified according to the clinical manifestations or genetic nosology. To date, 40 SCAs have been characterized, and include SCA1–40. The pathogenic genes of 28 SCAs were identified. In recent years, with the widespread clinical use of next-generation sequencing, the genes underlying SCAs, and the mutants as well as the affected phenotypes were identified. These advances elucidated the phenotype–genotype relationship in SCAs. We reviewed the recent clinical advances, genetic features and phenotype–genotype correlations involving each SCA and its differentiation. The heterogeneity of the disease and the genetic diagnosis might be attributed to the regional distribution and clinical characteristics. Therefore, recognition of the phenotype–genotype relationship facilitates genetic testing, prognosis and monitoring of symptoms.

Conflict of interest

The authors report no conflicts of interest.

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Spinocerebellar ataxia (SCA) consists of a large group of heterogeneous inherited neurodegenerative disorders that are characterized by progressive cerebellar ataxia with oculomotor abnormalities, dysarthria, pyramidal and extrapyramidal signs, pigmentary retinopathy, peripheral neuropathy, cognitive dysfunction and other symptoms (1).The group of diseases was designated as autosomal dominant cerebellar ataxias (ADCAs) and classified into three types according to their clinical manifestations (2). SCAs were also classified according to the genetic nosology (3). To date, 40 types of SCAs have been identified and are classified as SCA1 through SCA40, most of which were categorized according to ADCA types (Table 1).

The prevalence of ADCA in the general population was estimated at 0.001–0.005% (4, 5). Ruano found that the prevalence of ADCA in Netherlands was 3.0/100,000 inhabitants (6), 4.2/100,000 in south Norway (7), 5.6/100,000 in Portugal (8), 1.9/100,000 in Brazil (4, 9), and 2.3/100,000 in Padua (Italy) (10). In Korea, the prevalence of hereditary cerebellar ataxia was 4.99/100,000 (11). No data were reported from China.

Similarly, the frequency of each SCA type varied regionally (12). For example, in Chinese ADCA, SCA3

Table 1. Clinical and genetics features of SCAs subtypes

SCAs	Mean AAO	Average years of course (range)	Specific symptoms	Locus	Gene	Protein	Trinucleotide repeat/mutation	Normal range	Fully penetrance range
ADCA type I									
SCA1	37 (4–74)	15 (10–30)	Hypermetric saccades, pyramidal signs, peripheral neuropathy	6p23	*ATXN1*	ataxin1	CAG (CAT)	6–44	39–91
SCA2	32 (1–66)	10 (1–30)	Slow saccadic eye movements, hyporeflexia, myoclonia, Parkinsonism syndrome	12q24	*ATXN2*	ataxin2	CAG	14–31	33–202
SCA3	36 (4–70)	21 (6–29)	Nystagmus, pyramidal signs, peripheral neuropathy, ophthalmoparesis, bulging eyes, fasciculations of the face and tongue, amyotrophy, extrapyramidal signs	14q21	*ATXN3*	ataxin3	CAG	12–44	52–86
SCA4	40–50 (19–59)	Slow progression	Sensory axonal neuropathy, hyporeflexia	16q22.1	UN	UN	UN	UN	UN
SCA8	39 (1–65)	Life long	Hyperactive tendon reflexes, decreased vibratory sense, cognitive deficits	13q21	*ATXN8OS/ATXN8*	–/ataxin 8	CTG/CAG	15–50	80–250
SCA10	36 (12–48)	9	Seizures, cognitive dysfunction	22q13	*ATXN10*	ataxin 10	ATTCT	10–32	800–4500
SCA12	33 (8–55)	UN	Parkinsonian features, dementia, action tremor	5q32	*PPP2R2B*	Protein phosphatase 2	CAG	4–32	51–78
SCA13	Infancy to 60	Life long	Moderate mental retardation, occasional seizure	19q13	*KCNC3*	Voltage-gated potassium channel 3	MM	–	–
SCA14	34 (3–70)	Life long	Axial myoclonus, cognitive impairment, tremor, mild sensory loss	19q13	*PRKCG*	Protein kinase C gamma type	MM, splicing mutation, deletion, indels	–	–
SCA15/16	26 (7–66)	31 (10–54)	Slow progression, mild hyperreflexia, tremor	3p26	*ITPR1*	Inositol triphosphate receptor type I	MM, deletion	–	–
SCA17	35 (3–75)	>8	Dementia, involuntary movements, psychiatric symptoms, dystonia	6q27	*TBP*	TATA-box-binding protein	CAG/CAA	25–40	49–66

Table 1. Continued

SCAs	Mean AAO	Average years of course (range)	Specific symptoms	Locus	Gene	Protein	Trinucleotide repeat/mutation	Normal range	Fully penetrance range
SCA18	15 (13–27)	Slow progression	Motor and sensory neuropathy, muscle weakness atrophy, decreased vibratory and proprioceptive sense	7q31–q32	*IFRD1*	Interferon-related developmental regulator 1	MM	–	–
SCA19/22	34 (11–45)	UN	Cognitive impairment, myoclonus, tremor	1p21–q21(23)	*KCND3*	Voltage-gated potassium channel Kv4.3	MM, deletion	–	–
SCA20	47 (19–64)	Slow progression	Palatal tremor, abnormal phonation, dentate calcification on computer tomography (CT)	11q12	UN	UN	UN	UN	UN
SCA21	17 (6–30)	Slow progression	Extrapyramidal signs (rigidity, akinesia), hyporeflexia, cognitive impairment	7p21-p15	*TMEM240*	Transmembrane protein 240	MM, truncating mutation	–	–
SCA23	50 (43–56)	Slow progression	Distal sensory neuropathy, pyramidal signs, proximal paresis of the legs, tremor	20p13	*PDYN*	Prodynorphin	MM	–	–
SCA25	1.5-39	UN	Peripheral sensory neuropathy, areflexia, gastrointestinal problems	2p21-p13	UN	UN	UN	UN	UN
SCA27	15-20	Life long	Tremor, subtle orofacial dyskinesia, pes cavus, mild axonal sensory neuropathy	13q34	*FGF14*	Fibroblast growth factor 14	MM, deletion	–	–
SCA28	24 (3–60)	Slow progression	Hyperreflexia, ptosis, ophthalmoparesis	18p11	*AFG3L2*	ATPase family gene 3-like 2	MM	–	–
ADCA type II									
SCA7	35 (0.5-60)	20 (1–45)	Retinal degeneration/visual loss	3p21-p12	*ATXN7*	ataxin7	CAG	4–19	36–460
ADCA type III									
SCA5	30 (10–68)	>25	Pure ataxia, tremor, nystagmus	11q13	*SPTBN2*	Beta-III spectrin	MM, deletions	–	–

Table 1. Continued

SCAs	Mean AAO	Average years of course (range)	Specific symptoms	Locus	Gene	Protein	Trinucleotide repeat/mutation	Normal range	Fully penetrance range
SCA6	43-52 (19–71)	Life long	Pure ataxia, slow progression	19p13	*CACNA1A*	P/Q voltage-dependent calcium channel	CAG	4–18	20–33
SCA11	30 (15–70)	Life long	Pure ataxia	15q15	*TTBK2*	Tau tubulin kinase-2	deletions, insertions	–	–
SCA26	42 (26–60)	Slow progression	Pure ataxia	19p13	*EEF2*	Eukaryotic translation elongation factor 2	MM	–	–
SCA29	Early childhood	UN	Pure ataxia	3p26	*ITPR1*	Inositol triphosphate receptor type I	MM	UN	UN
SCA30	52 (45–76)	UN	Pure ataxia	4q34-q35	UN	UN	UN	UN	UN
SCA31	58 (8–83)	UN	Pure ataxia, progressive sensorineural hearing impairment	16q21	*BEAN1*	Brain-expressed protein associating with Nedd4 homolog	TGGAA	1.5–2.0 kb	2.5–3.8 kb
Others									
SCA32	Adulthood	UN	Cognitive impairment, azoospermia in male	7q32-q33	UN	UN	UN	UN	UN
SCA34	Infant onset	UN	Neurocutaneous syndrome, decreased reflexes	16p12-q16	*ELOVL4*	Elongation of very long chain fatty acids protein 4	MM	–	–
SCA35	44 (40–48)	Slow progression	Pseudobulbar palsy, tremor, hyperreflexia, torticollis-reduced position sense	20p13	*TGM6*	Transglutaminase6	MM	–	–
SCA36	53 (39–65)	UN	Motor neuron dysfunction, acoustic impairment	20p13	*NOP56*	Nucleolar protein 56	GGCCTG	3–8	1700–2300
SCA37	48 (38–64)	Slow progression	Abnormal ocular movements	1p32	UN	UN	UN	UN	UN
SCA38	40 (34–51)	Slow progression	Adult onset; pure spinocerebellar ataxia; axonal neuropathy	6p12	*ELOVL5*	Elongation of very long chain fatty acids protein 5	MM	–	–
SCA40	43 (42–43)	–	Adult onset; spasticity	14q32	*CCDC88C*	Coiled-coil domain containing 88C	MM	–	–

AAO, age at onset; MM, missense mutation; SCA, spinocerebellar ataxia; UN, unknown.

accounted for 54.6–72.5% (13, 14), followed by SCA2 (5.7–6.7%), SCA1 (5.9%), SCA6 (1.6–3.3%), and SCA7 (0.8–4.8%) (14, 15), while in Brazil, SCA3 accounted for 92%, followed by SCA7 (2%), and certain rare types.

The genes underlying 28 out of the 40 types of SCAs including SCA1–3, 5–8, 10–14, 15/16, 17, 18, 19/22, 21, 23, 26–29, 31, 34–36, 38 and 40 have been identified (OMIM, https://www.ncbi.nlm.nih.gov/books/NBK1138/). The loci of the other six SCAs, including SCA4, 20, 25, 30, 32, and 37, were located by linkage disequilibrium. The SCA4 locus was present in the same region as SCA31 (16). SCA9, 33 and 39 were unassigned. SCA24 was recessively inherited. The pathogenic genes or genetic loci of SCA1-40 are summarized in Table 1.

Although SCAs are highly heterogeneous, the clinical manifestations are significant and obvious. We reviewed the phenotype–genotype relationship of SCAs from the clinical perspective of ADCA to facilitate the neurological differentiation and clinical diagnosis of SCA.

ADCA type 1

ADCA type 1 manifests cerebellar ataxia combined with ophthalmoplegia, dementia, extrapyramidal signs, optic atrophy and amyotrophy.

SCA1, SCA2, SCA3 and SCA17

SCA1, 2, 3 and 17 are caused by dynamic mutations in coding regions, with distinct characteristics.

SCA1 is commonly seen in Italian (41%), South African (40.7%), Australian (16%), German (9%), Chinese (7%), Korean (12%), Japanese (5.5%) and Spanish (6%) populations. SCA2 is more often seen in Italy, India, Mexico and Cuba with a frequency ranging from 24% to 45.4%. The frequency of SCA3 is high in France, USA, Japan, Portugal, Brazil and China, ranging from 20.4% to 92%. SCA17 has been reported in Japanese, Germans, French, Chinese, Koreans, Italian Mexicans, Greeks and Indians, albeit with a frequency much lower than SCA1–3 (13, 17–28).

The cerebellar ataxia associated with SCA3 includes a wide range of clinical manifestations: pyramidal signs, peripheral neuropathy, ophthalmoparesis and bulging eyes, fasciculations of the face and tongue, amyotrophy, and extrapyramidal signs, and, rarely, dementia. The heterogeneity presents in terms of age at onset (AAO), clinical manifestations and symptoms. SCA3 is caused by an unstable CAG triplet repeat expansion of exon 10 in *ATXN3*. Generally, it is classified into three types based on the spectrum of clinical manifestations and CAG repeat size (29, 30). The SCA3 types containing early AAOs and higher number of CAG repeats tend to exhibit a pyramidal phenotype and dystonia, whereas those with late AAOs and smaller CAG repeat numbers are probably to develop neuropathy (31, 32). Subsequent studies described five subtypes: type 4 comprising a Parkinsonian triad, type 5 including spastic paraparesis, type 6 manifesting pure cerebellar ataxia and type 7 associated with a mixed form of ataxia and levodopa responsive Parkinsonism (33). Other rare manifestations have been reported, including retinal degeneration, complicated hereditary spastic paraplegia, stiff-person syndrome, motor neuronal disease, akathisia, verbal fluency and visual memory deficits, dystonia, involuntary movement combined with memory decline, and hearing loss (32, 34–39). However, no significant difference was found between these sub-phenotypes and CAG repeat expansions (33). The homozygous patients showed a more serious course (40).

SCA1 and SCA2 are also characterized with features of progressive ataxia starting in the mid-adulthood. The SCA2 and SCA3 types were more frequently associated with basal ganglia symptoms. Bulging eyes were predominantly seen in SCA3 (41). Decreased deep tendon reflexes were observed more frequently in SCA2, and more commonly increased in SCA1 and SCA3. Recent studies found that SCA1 progressed faster than SCA2 and SCA3 (42, 43). The eye movements in these three SCAs were distinct. In SCA2, saccade velocity was markedly decreased, but gaze-evoked nystagmus was not associated. In SCA3, square wave jerks were exclusively observed and gaze-evoked nystagmus was often present. In SCA1, nystagmus was more common and saccade amplitude was significantly increased, resulting in hypermetria (44, 45).

The SCA2 allele carrying 32 repeats represented an intermediate allele compared with the normal (14–31 repeats) and fully penetrant alleles (33–202 repeats) (46). The allele with 33 CAG repeats was considered a ‘late onset’ allele. The expansion was interrupted by a CAA repeat. Parkinsonism is often seen in SCA2 (SCA2-P). Compared with cerebellar ataxia type (SCA2-A), the SCA2 is associated with a mild CAG repeat expansion (32–42) usually interrupted by a CAA repeat (47). The SCA2-A harbored a CAG expansion without CAA interruption (48, 49). Recent linkage analysis and whole-exome sequencing indicated that the CAG expansion was the only causative mutation responsible for SCA2-P (50).

Interestingly, recent studies investigated the pleiotropism of expanded *ATXN-2*. The fully expanded *ATXN-2* caused both frontotemporal dementia-amyotrophic lateral sclerosis (FTD-ALS) and SCA2 in different family members of a single family (51, 52).

The homozygous state of SCA2 was reported to alter the phenotype and exacerbate disease, without affecting the AAO (53).

The anticipation of SCA17 was infrequently documented (54). The AAO and CAG/CAA repeat sizes are inversely related (53, 55), but not as strongly as in other dynamic disease mutations. SCA17 is referred to as Huntington’s disease-like syndrome type 4 (HDL-4), with typical chorea, dementia and psychiatric dysfunction. Further, pyramidal signs and epilepsy are prominent features (56). A few phenotypes are related to the number of CAG/CAA repeats. Parkinsonism and chorea are associated with small size (42–48), while pyramidal signs and dystonia are common in larger-sized amplification

(≥50) (57). Cerebellar ataxia and reduced intellectual function/psychiatric symptoms are commonly seen regardless of the size.

SCA8, SCA10, and SCA12

The nucleotide repeat expansions of SCA 8, 10, and 12 are located in the non-coding regions, and the alleles are partially characterized by dynamic mutations. SCA8 usually occurs in adulthood and progresses slowly with cognitive decline, pyramidal and sensory signs (58). The SCA8 phenotype is relatively varied compared with other SCAs, because of the atypical non-cerebellar symptoms of Parkinsonism, ALS and migraine (59). It is attributed to CTA and CTG triplet repeat expansion in *ATXN8OS/ATXN8*. No relationship was observed between the expanded repeats and AAO, disease progression or disease severity (60). Reduced penetrance occurred in SCA8. The expansion carriers remain asymptomatic for ataxia and the incidence of disease was not predicted by the length of expansion. Therefore, genetic counseling is critical to explaining the results in asymptomatic individuals or family members (61).

SCA10, manifesting cerebellar ataxia and epilepsy, occurs in Mexican (about 15% of ADCA, following SCA2) and Brazilian populations (0.7–11.6% of ADCA, following SCA3) (23, 62, 63). Patients diagnosed in Argentinian and Latin American families were attributed to ATTCT repeats in *ATXN10*. Recent studies proposed penta- and heptanucleotide 'ATCCT interruptions', involving SCA10 expansions (64, 65). The expansion size and AAO were inversely related only in SCA10 without interruptions. Interrupted expansion alleles showed anticipation but paradoxically contracted during transmission, particularly in paternal lineages. The presence of repeat interruption increased the risk of epilepsy, and its prognosis during genetic counseling.

SCA12 is rare worldwide. In addition to a few families in India (66), it was detected in one American family of German origin, one Singaporean family, two Italian families and three Chinese pedigrees. Recently, we reported three SCA12 families, suggesting that the incidence of SCA12 in Chinese population might be higher than previously reported (67). SCA12 is caused by a CAG repeat expansion in *PPP2R2B*. Because of the limited case number, the number of pathological mutations exceeds 51. However, one of our recent reported cases carried 46 CAG repeats, which might be the shortest pathogenic number of SCA12 (67).

The triplet, quintuplet or sextuplet repeats expansion in non-coding region (including SCA36 discussed later) do not directly encode a toxic protein but affect the cellular functions via RNA loss-of-function, RNA gain-of-function or repeats associated with non-ATG (RAN) translation (only in SCA8) (68, 69), resulting in deregulation of gene transcription and expression (70), formation of 'RNA foci' in the nucleus and negative impact on cellular function (71–73). In contrast, the SCAs expansion involving the coding region were mostly attributed to gain-of-function involving toxic mutant proteins affecting cellular function (74, 75).

SCA13, SCA14, SCA15, SCA18, SCA19/22, SCA21, SCA23, SCA27, and SCA28

SCA13, 14, 15, 18, 19/22, 21, 23, 27 and 28 are caused by conventional mutations. However, the number of families with SCAs in this group is not adequate to obtain genotype–phenotype correlations. The following results were observational.

With respect to SCA13, the p.R420H (c.G1260A) mutation in *KCNC3* is associated with late-onset ataxia, whereas the p.F448L (c.C1344A) and p.R423H (c.G1268A) mutations are related to early-onset ataxia, delayed motor milestones, mental retardation and epilepsy (76, 77). In SCA14, the same mutation presented different symptoms, even in a single family (78, 79). In SCA28, p.M666R (c.T1997G) and p.E700K (c.G2098A) mutations were identified in early-onset patients, and another mutation was related to adult-onset (80). SCA15 is rare and accounted for 1% of ADCA in Caucasian population and 0.1% in Japan (24, 81). It is characterized by slow progression with variable AAO. It is characterized by tremors, cerebellar atrophy, occasional pyramidal signs, cognitive impairment and involuntary movements (82, 83). It is caused by the *ITPR1* deletion or missense mutation. The missense mutations in *ITPR1* also cause SCA29, which is discussed later in ADCA type 3.

No explicit phenotype–genotype relationships were observed for SCA18, 21, 23, or 27 because of their rarity. Their clinical and genetic features are listed in Table 1.

ADCA type 2

SCA7 is the only type of ADCA type 2, which is characterized by progressive cerebellar ataxia and retinal degeneration. The disease course spanned four stages in a recent longitudinal study. Electroretinograms were identified as biomarkers of disease onset and progression (84). SCA7 is rare, but is often found in Swedish, Finnish, and South African (22.2%) populations as well as in Brazilian (6%), Spanish (1%), Portuguese (1%) and Australian (2%) populations (17–27).

SCA7 is caused by CAG triplet repeat expansions in *ATXN7*. A higher CAG repeat number is associated with an earlier AAO, more severe symptoms, rapid clinical progression and a high frequency of diseased vision (85, 86). The expansion was highly unstable during transmission, and anticipation was clear. The mean increase in CAG repeat number was reported to be 10 ± 16. Instability was significantly greater in male transmission (87).

ADCA type 3

ADCA type 3 is considered a 'pure' cerebellar ataxia, in which SCA6 is the most common followed by SCA31.

SCA6 was commonly seen in Korean (15–23%), Japanese (6–23%), Dutch (11–23%), Australian (17%)

and German populations (10–22%), and less frequently seen in the UK (5%), India (0–4%), and China (0–3%) (17–27, 88). It is caused by CAG triplet expansion in *CACNA1A* (89). The expanded CAG repeat number is inversely correlated with AAO. The size of SCA6 expanded alleles is generally stable during transmission, and anticipation is rare. A dosage effect was observed (90–93).

SCA6 together with episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM1) represents a clinical continuum attributed to *CACNA1A* mutations. EA2 is an autosomal dominant disorder characterized by episodic attacks of ataxia (94). EA2 and FHM1 are usually caused by missense, deletion or insertion mutations while SCA6 are caused by CAG triplet expansions (http://www.hgmd.cf.ac.uk/). Interestingly, the clinical manifestations of SCA6, EA2 and FHM presented in different members of a single family with either CAG triplet number expansion (94) or missense mutations (95, 96), or even in the same patient (97, 98).This phenomenon was explained by similar underlying mechanisms of functional changes in calcium channel subunits encoded by mutant *CACNA1A*. The SCA6 polyglutamine mutation in *CACNA1A* has been shown to affect channelopathy and transcriptional regulation (99). The point mutations also affected the channelopathy and transcriptional regulation (94). However, the underlying mechanism was obscure and needs further investigation.

Most cases of SCA31 were reported in Japan, while three cases represented Chinese, Korean and Brazilian populations (100–102). It is a late-onset cerebellar ataxia usually associated with hearing loss. It is also associated with extracerebellar pyramidal signs, extrapyramidal signs, dizziness or psychiatric ailments. It is attributed to complex penta-nucleotide repeats containing (TGGAA)n inserted in the introns of *BEAN1*. The size of the insertion was inversely correlated with AAO in patients ($r = -0.41$), although it may not affect the progression after onset (103). Very mild anticipation and subtle expansion were also observed (104).

Despite the association of SCA6 and SCA31 with similar type of ADCA, differences were still observed. The AAO was higher in SCA31 than in SCA6. In several reports of Japanese population, the number of extracerebellar symptoms varied between SCA31 and SCA6. Gaze-evoked nystagmus and downbeat positioning nystagmus were more frequent in SCA6 than in SCA31, and successfully differentiated SCA6 from SCA31 (105). In neuroimaging, cerebellar atrophy started from the upper vermis in magnetic resonance image (MRI) of SCA31, while in SCA6, the fourth ventricle was enlarged even in the early stage of disease (106).

SCA5 has been reported in five families worldwide including American, French, German, Japanese and Norwegians and in one congenital SCA5 patient (107, 108). It is late-onset and usually does not shorten the life span (108). Six different mutations including three in-frame deletions and three missense mutations related to SCA5 have been found in *SPTBN2*. SCA11 was also rare. Four families were reported from 1999 (26, 100), and none involved Chinese population (27). Two in-frame deletions and one missense mutation were confirmed as pathogenic (109). Because of the rarity of SCA5 and SCA11, no explicit phenotype–genotype relationships were observed.

SCA29 is also known as congenital non-progressive cerebellar ataxia, first reported in 1987 (110). The causative gene was found by exome sequencing in 2012. Until now, p.N587D (c.A1759G) and p.V1547M (c.G4639A) have been reported pathogenic. Recently, four unrelated sporadic infant-onset non-progressive cerebellar ataxia were attributed to *de novo* missense mutations in *ITPR1*, suggesting the existence of three types of *ITPR1*-related SCAs: SCA15, SCA29 and sporadic one (111). The features of SCA26 were referred to Table 1.

SCA34, SCA35, SCA36, SCA38 and SCA40

SCA34 is associated with the onset of erythremia and hyperkeratosis in early childhood. Cerebellar ataxia manifests in mid-adulthood and progresses slowly. Skin lesions tend to improve with age. The pathogenic gene was identified in 2015 by genome-wide linkage analysis and next-generation sequencing and incomplete penetrance was found (112).

SCA36 is rare worldwide, accounting for 1.9% of all French SCAs, 1.5% of all Japanese SCAs and 1.6% in Chinese ADCA (113). It is characterized by cerebellar ataxia with progressive motor neuronal dysfunction and sensorineural hearing loss (72, 114). Cognitive and affective impairments and oromandibular dystonia were also reported (115–117). The expansion of intronic GGCCTG hexanucleotide repeat in *NOP56* causing SCA36 was identified in 2011 (118). The expansion tended to increase during transmission, with larger expansions resulting in more severe symptoms (119). However, one recent report found that small expansions (25, 30 and 31, respectively) caused the disease. The clinical features were indistinguishable between individuals with short and typically long expansions (120).

The causative genes of SCA38 and 40 were identified by genome-wide genetic studies (121). The clinical and genetic features of SCA35 are listed in Table 1.

MRI of SCAs

MRI is helpful to the diagnosis of SCAs. Atrophy in cerebellum, pon, brain stem, basal ganglia or certain cortical areas was the main feature on MRI (122). In some types, like SCA5, 8 (123), 10, (124), 11, 13, 14, 15/16, 20, 27 and 28, atrophy was restricted within cerebellum (122). SCA12 was found atrophy in cerebellum and/or cerebrum (66). The brain atrophy in SCA1, 2, 3, 6, 7, 17 was wide. SCA1 showed atrophy mainly in brainstem, cerebellum, basal ganglia and cortex. SCA2 showed atrophy in cerebellum, pons, medullar oblongata, spinal cord and also in parietal cortex and thalamus. SCA6 showed severe atrophy in cerebellum, mild atrophy in pons, basal ganglion and cortex. SCA7 and 17 had obvious atrophy in brainstem

and the cortical area was affected. As for SCA36, atrophy was found in initial stage and global cerebellar atrophy and oliveo-ponto-cerebellar atrophy showed by the disease progression (72, 119).

Conclusion

The phenotype–genotype correlation facilitates clinical and differential diagnosis of SCA, prediction of disease course and monitoring of symptoms and genetic counseling. Advances in molecular diagnostics may unravel additional disease-causing genes in SCAs. Detection of the genetic risk loci modifying the phenotype will elucidate the clinical pattern and highlight the underlying pathogenesis.

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