Massive expansion of SCA2 with autonomic dysfunction, retinitis pigmentosa, and infantile spasms

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ABSTRACT

Objective: To provide clinical data on a cohort of 6 patients with massive expansion (>200 CAG repeats) of spinocerebellar ataxia type 2 (SCA2) and investigate possible pathways of pathogenesis using bioinformatics analysis of ATXN2 networks.

Methods: We present data on 6 patients with massive expansion of SCA2 who presented in infancy with variable combinations of hypotonia, global developmental delay, infantile spasms, and retinitis pigmentosa. ATXN2 is known to interact with a network of synaptic proteins. To investigate pathways of pathogenesis, we performed bioinformatics analysis on *ATXN2* combined with known genes associated with infantile spasms, retinitis pigmentosa, and synaptic function.

Results: All patients had a progressive encephalopathy with autonomic dysfunction, 4 had retinitis pigmentosa, and 3 had infantile spasms. The bioinformatics analysis led to several interesting findings. First, an interaction between ATXN2 and SYNJ1 may account for the development of retinitis pigmentosa. Second, dysfunction of postsynaptic vesicle endocytosis may be important in children with this progressive encephalopathy. Infantile spasms may be associated with interactions between ATXN2 and the postsynaptic structural proteins MAGI2 and SPTAN1.

Conclusions: Severe phenotype in children with massive expansion of SCA2 may be due to a functional deficit in protein networks in the postsynapse, specifically involving vesicle endocytosis. *Neurology*® 2011;77:1055–1060

GLOSSARY

GO = gene ontology; **ISS** = infantile spasms; **OFC** = occipital-frontal circumference; **RP** = retinitis pigmentosa; **SCA2** = spinocerebellar ataxia type 2.

Spinocerebellar ataxia type 2 (SCA2) is an autosomal dominant disease associated with expansion of a CAG repeat in *ATXN2*.[1] An expansion size of 33–64 repeats results in adult onset of slowly progressive ataxia, dysarthria, and eye movement abnormalities.[2] Other phenotypes in adults have included retinitis pigmentosa (RP),[3–5] autonomic disturbance,[6] hypogonadotropic hypogonadism,[7] and mixed ataxia–parkinsonism.[8,9] There are reports of childhood-onset SCA2 with expansions of 62–75 repeats,[10–13] and in some families variation in *CACNA1A* modifies age of onset.[14]

Moderate-sized expansion in *ATXN2* results in Purkinje cell degeneration through cellular dysfunction on multiple levels,[15–17] and may include abnormalities in RNA binding and splicing.[18] Mice with polyQ-58 mutations in *Atxn2* have Purkinje cell degeneration similar to that seen in patients with adult-onset SCA2.[19] Interestingly, knockout mice deficient in *Atxn2* are obese and have abnormal fear conditioning, but have normal neurohistology.[20]

A single pediatric patient report associated massive expansion (>200 repeats) of SCA2 with progressive encephalopathy, optic atrophy, RP, and early death.[21] We present data on 5 additional patients, including updated clinical information on the patient previously reported. All

Supplemental data at www.neurology.org

Supplemental Data

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had massive expansion of SCA2 with cortical and cerebellar degeneration, 4 had RP, 3 had infantile spasms (ISS), and 2 others had infant-onset epilepsy. We then used bioinformatics tools to generate hypotheses about mechanisms of pathogenesis. Given the interaction of ATXN2 with a synaptic protein-protein network[18] that includes A2BP1,[22] and the association of A2BP1 with epilepsy and autism,[23,24] we asked whether a network relationship might exist between the ATXN2 network, the identified genetic causes of RP, the newly described genes associated with ISS, and other pathways of synaptic function. We hypothesize that the severe phenotype of patients with massive expansion of SCA2 may be due to a functional deficit in key protein–protein networks in the postsynapse.

METHODS **Patients.** Retrospective records from 6 patients with massive expansion of SCA2 were reviewed, including EEG reports, brain imaging, and histopathology. Analysis of the SCA2 alleles was carried out as described[1] with additional modifications.[25]

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review board of the University of Chicago.

Bioinformatic analyses. ***Role of ATXN2 network in brain development and function.*** The genes in the ATXN2 interaction network were investigated for evidence of brain expression and role in brain development and function using publicly available Web-based resources, as detailed in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

Network analysis. The genes in the ATXN2 interaction network were next combined with 1) a list of genes associated with RP; 2) a list of genes associated with ISS; and, given the known interactions between ATXN2 and synaptic proteins, 3) a list of genes involved in synaptic function. Each combined list was then examined with a network analysis algorithm to look for evidence of interactions between the ATXN2 network and genes/proteins associated with RP, ISS, and synaptic function, as detailed in appendix e-1.

RESULTS **Patient 1.** This infant girl was previously reported.[21] She presented with apnea at 2 weeks. Occipital-frontal circumference (OFC) was −3 SD at 10 months of age. Ophthalmologic examination showed RP. SCA2 testing revealed an abnormal allele with 220 CAG repeats. However, one aspect of her case not known to the authors of the initial report was that she developed ISS at 16 months, with hypsarrhythmia on EEG. She died at 2 years from respiratory complications.

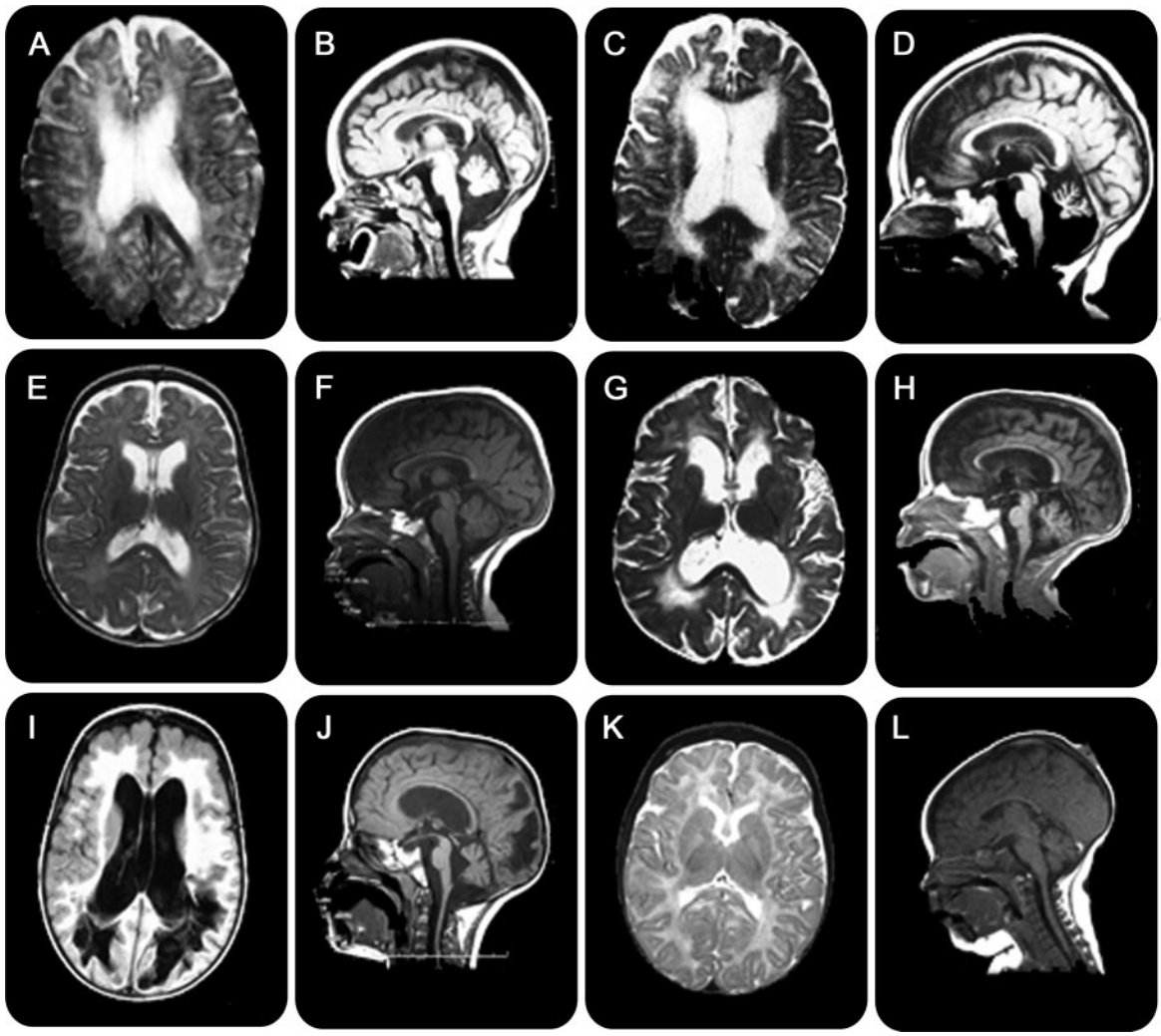
Patient 2. This infant girl presented with hypotonia at 6 months. MRI at 7 months (figure 1, A and B) showed probable cerebellar atrophy and delayed myelination. At 14 months she developed ISS with hypsarrhythmia. She had relative microcephaly (length 25th percentile, OFC −2 SD) and optic nerve atrophy. Repeat brain MRI at 17 months (figure 1, C and D) showed cerebral dysmyelination, enlarged lateral ventricles, and obvious cerebellar and brainstem atrophy. SCA2 testing showed CAG repeat size of >200. She had autonomic dysfunction, and died at 22 months from aspiration pneumonia.

Patient 3. This infant boy presented at 3 months with focal seizures. At 10 months he developed ISS with hypsarrhythmia. Brain MRI at 10 months showed prominent sulci frontally, enlargement of the lateral and third ventricles, and an atrophic-appearing cerebellum (not shown). At 12 months he was microcephalic, with sluggish pupillary reaction to light. Ophthalmologic examination diagnosed cortical visual impairment, and otoacoustic emissions were absent. He had impaired swallowing and autonomic instability. SCA2 testing showed a repeat length of >200. He died at 13 months.

Patient 4. This infant girl presented with loss of head control and poor visual fixation at 3 months and at 5 months she had myoclonic seizures. At 17 months EEG showed high-amplitude bursts of slow waves with polyspikes reminiscent of hypsarrhythmia. Brain MRI at 6 months showed diffuse parenchymal volume loss and delayed myelination (figure 1, G and H). She was microcephalic (OFC −3 SD) and by 21 months was somnolent with minimal visual interaction. Ophthalmologic examination showed RP. SCA2 testing showed an expanded allele with >500 CAG repeats. She died at 32 months. Pathologic examination of the cerebellum showed reduction in the thickness of the molecular layer, but relative preservation of both Purkinje and granular neurons (figure 2A).

Patient 5. This infant girl was the paternal half-sister of patient 4. She had global developmental delay in infancy and was reported to be microcephalic (OFC not available). At 4 years she was failing to thrive with poorly coordinated swallow and 10 months later began to lose motor and cognitive milestones and had autonomic dysfunction. Brain MRI at 5 years 10 months (figure 1, I and J) showed diffuse T2 white matter signal abnormalities, with cavitations of the parieto-occipital lobes and cortical and cerebellar volume loss. Ophthalmologic examination revealed

Figure 1 Brain MRI scans of patients with massive expansion of SCA2



Axial (A) and sagittal (B) views of patient 2 at 7 months, showing enlarged lateral ventricles, and small brainstem and cerebellum. By 17 months, axial (C) and sagittal (D) views show progression of cerebral white matter volume loss and dysmyelination, and pontocerebellar atrophy. Axial (E) and sagittal (F) views of patient 4 at 6 months and again (G) and (H) at 19 months showing worsening cerebral volume loss, abnormal white matter signal, thinning of the corpus callosum, and pontocerebellar atrophy. Axial (I) and sagittal (J) views of patient 5 at 5 years 10 months showing diffuse T2 white matter signal abnormalities, with parieto-occipital cavitations, thinning of the corpus callosum, and cerebellar volume loss. Axial (K) and sagittal (L) views of patient 6 at 12 months showing mild volume loss of the anterior cerebellar vermis.

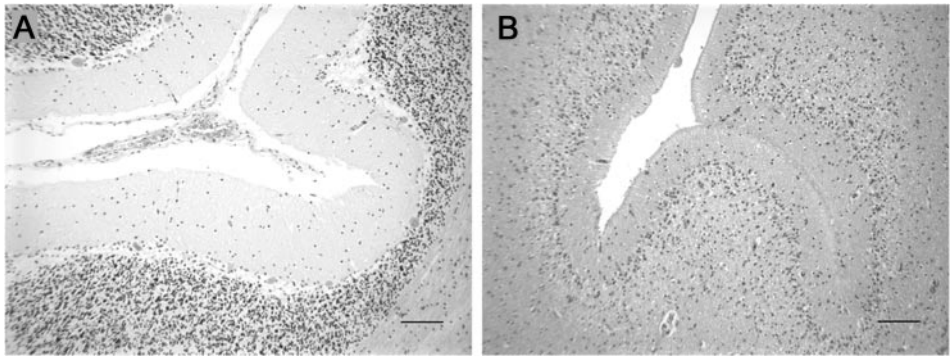
optic nerve atrophy and RP. Initial SCA2 testing was negative, but was repeated due to suspicion that routine PCR amplification may not detect very large expansions, with discovery of a median CAG repeat length of 750.

Patient 6. This infant girl presented at 2 months with poor head control and lack of visual fixation. At 7 months she had tonic seizures. An EEG at 14 months showed multifocal epileptiform discharges. At 12 months she was diagnosed with RP. Brain MRI at 12 months (figure 1, K and L) showed mild cerebellar atrophy. At 13 months a gastrostomy tube was placed. SCA2 testing showed 300 CAG repeats. The patient died after a neurodegenerative course. Pathologic examination of the cerebellum showed profound loss of Purkinje and granular neurons with severe attenuation of the molecular layer (figure 2B). The data on all 6 patients are summarized in table 1.

Bioinformatic analyses. ***Role of ATXN2 network in brain development and function.*** The evidence for each gene in the *ATXN2* network for a role in brain development and function is shown in table e-1 (see appendix e-1). This analysis validated the importance of several members of the ATXN2 network in gene ontology (GO) categories important for neurologic development and function.[18,26]

Network analysis. Analysis of the genes in the ATXN2 network combined with genes associated with RP did not reveal any direct interactions (data not shown). However, a network relationship be-

Figure 2 Pathologic examination of cerebellum of a patient with massive expansion of SCA2



Photomicrograph (A) of the cerebellar cortex from patient 4. There is a reduction in the thickness of the molecular layer, but relative preservation of both Purkinje and granular neurons. Photomicrograph (B) of the cerebellar cortex from patient 6. There is profound loss of Purkinje and granular neurons with severe attenuation of the molecular layer. Both figures stained with hematoxylin and eosin. Scale bar = 100 μm.

tween ATXN2 and SYNJ1 suggests a possible mechanism for retinal dysfunction in patients with expansion of SCA2. As several patients in this series had ISS, we also looked for interactions between the ATXN2 network and the genes associated with ISS. A network was found between ATXN2, SYNJ1, PTEN, MAGI2, and SPTAN1 (figure 3). *MAGI2* is expressed postsynaptically, as is *ACTN2,* a key member of the ATXN2 network.[27,28] ACTN2 forms part of an interaction network with the spectrin protein SPTAN1, mutations of which have recently been described in children with ISS.[29] We then analyzed the ATXN2 network together with proteins involved in synaptic function, in order to discover additional interactions potentially involved in pathogenesis. Our analysis identified additional interactions between ATXN2 and SH3GL2, a member of the GO biological process of synaptic vesicle transport.

DISCUSSION Massive expansion of SCA2 is associated with a severe neurologic phenotype, with hypotonia and global developmental delay in the first year of life. Four of the patients in this report had RP, which has been described in some patients with moderate-sized SCA2 expansions as well. Our bioinformatics analysis identified a hypothetical network relationship between ATXN2 and SYNJ1. Synj1 has a role in zebrafish retinal function, specifically in cone photoreceptors,[30,31] and it is possible that impaired ATXN2-SYNJ1 interactions play a role in the development of RP in patients with expanded SCA2 alleles.

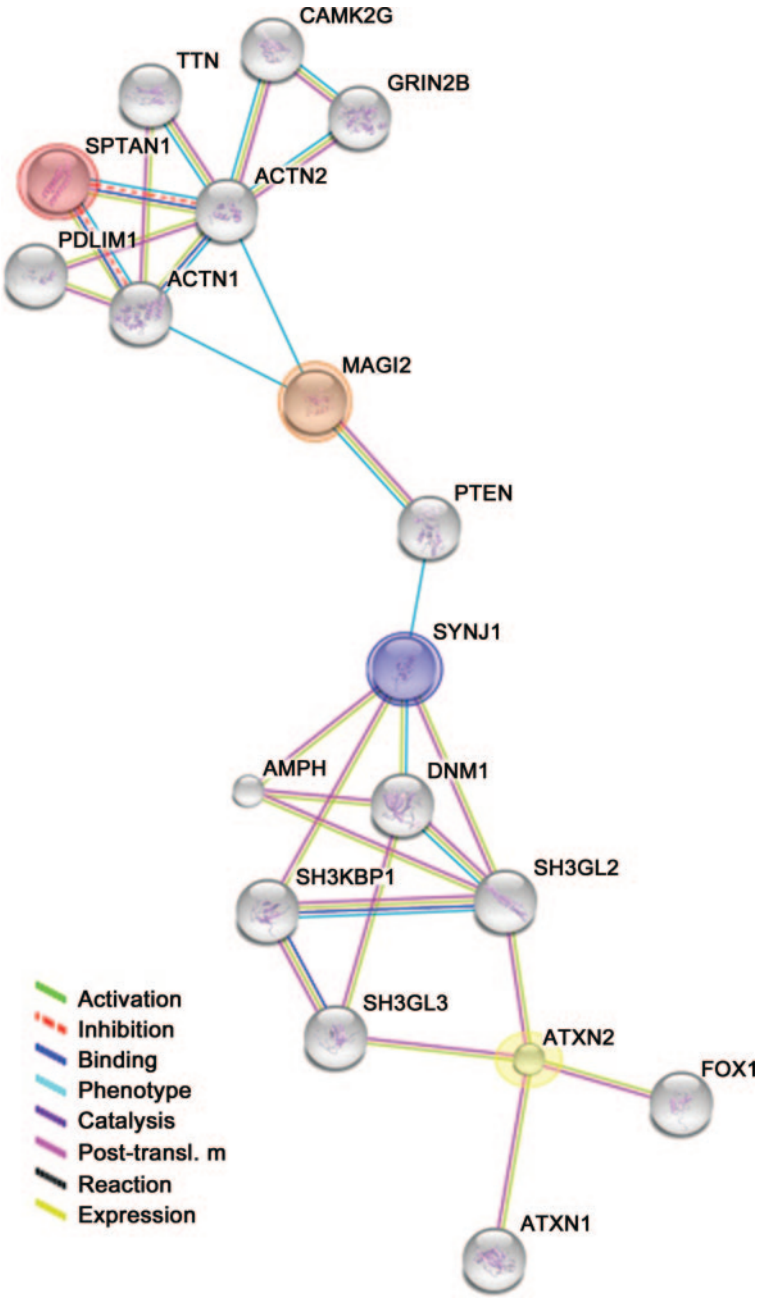
Three of the patients developed ISS, and one of the others had infant-onset myoclonic seizures with an EEG with elements of hypsarrhythmia. As ISS can be associated with mutations in genes with roles in forebrain development, specifically synaptic function,[29,32–35] we focused our bioinformatics analysis on discovery of further interactions between the ATXN2 network and proteins important in synapse biology. Previous work on the ATXN2 network[18,26] supported this approach, and we report additional possible interactions between ATXN2 and proteins involved in synaptic vesicle endocytosis, including SH3KBP1, SYNJ1, DNM1, and AMPH. SYNJ1 has an additional role in postsynaptic AMPA regulation,[36] and through interaction with PTEN connects

Table 1 Features of 6 children with massive expansion of SCA2

Patient	SCA2 repeat size	Affected parent/ SCA2 repeat size	GDD/age, mo	Eye exam	Seizures/age, mo	Autonomic dysfunction
1[a]	220	Father/43	+/7	RP, OA	ISS/16	+
2	>200	Father/42	+/2	OA	ISS/14	+
3	>200	Mother/45	+/3	CVI	Partial sz/3 ISS/10	+
4	500	Father/40	+/3	RP	Myoclonic sz/5	NK
5	~750	Father/40	+/~ 12	RP, OA	None	+
6	300	Father/43	+/2	RP	Tonic sz/7	+

Abbreviations: CVI = cortical visual impairment; GDD = global developmental delay; ISS = infantile spasms; NK = not known; OA = optic nerve atrophy; RP = retinitis pigmentosa; SCA2 = spinocerebellar ataxia type 2; SZ = seizures.
[a] Patient 1 previously reported.[21]

Figure 3 Postsynaptic protein–protein interaction network, showing relationship between ATXN2 (yellow) and SYNJ1 (blue) via SH3GL2 and SH3KBP1



SYNJ1 in turn has a relationship with PTEN. The postsynaptic proteins associated with infantile spasms, MAGI2 (orange) and SPTAN1 (red), form a subnetwork that in turn interacts with PTEN. Figure generated by STRING 8.3 with 0.9 confidence level.

to MAGI2, an anchoring molecule in the postsynaptic density associated with ISS.

It remains unclear why children with massive expansions in SCA2 have a more severe phenotype than patients with more moderate-sized expansions. The mechanism may involve a toxic effect of messenger RNA containing the expansion and impairment of key cellular survival pathways, similar to that found in myotonic dystrophy type 1.[37,38] We speculate that this pathway dysfunction may be most deleterious at the synapse. Further study will also be needed to clarify the variable clinical and neuropathologic spectrum seen in this disorder.

We report a severe neurologic phenotype in a group of 6 patients with massive expansion of SCA2. We used a bioinformatics approach to generate the hypothesis that a functional deficit in several important protein networks in the postsynapse may be involved in pathogenesis. This hypothesis can be tested in the repeat expansion mouse model of SCA2, with more severe phenotypes expected to correlate with abnormal expression patterns of proteins in the postsynapse.

AUTHOR CONTRIBUTIONS

Dr. Paciorkowski: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Shafrir: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Hrivnak: analysis or interpretation of data, acquisition of data. Dr. Patterson: drafting/revising the manuscript, contribution of vital reagents/tools/patients. Dr. Tennison: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Clark: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Gomez: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

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Karen Snow, MD, contributed patients to this series, but died in 2006 prior to the preparation of this publication.

DISCLOSURE

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REFERENCES

1. Pulst SM, Nechiporuk A, Nechiporuk T, at al. Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2. Nat Genet 1996;14:269–276.
2. Paulson HL. The spinocerebellar ataxias. J Neuroophthalmol 2009;29:227–237.
3. Rufa A, Dotti MT, Galli L, et al. Spinocerebellar ataxia type 2 (SCA2) associated with retinal pigmentary degeneration. Eur Neurol 2002;47:128–129.
4. Ragothaman M, Sarangmath N, Chaudhary S, et al. Complex phenotypes in an Indian family with homozygous SCA2 mutations. Ann Neurol 2004;55:130–133.
5. Ragothaman M, Muthane U. Homozygous SCA 2 mutations changes phenotype and hastens progression. Mov Disord 2008;23:770–771.

6. Montes-Brown J, Sánchez-Cruz G, García AM, Báez ME, Velázquez-Pérez L. Heart rate variability in type 2 spinocerebellar ataxia. Acta Neurol Scand 2010;122:329–335.
7. Kwon D, Park MH. Hypergonadotropic hypogonadism in spinocerebellar ataxia type 2: a case report. J Sex Med 2009;6:1779–1782.
8. Momeni P, Lu C, Chou YW, Chang H, et al. Taiwanese cases of SCA2 are derived from a single founder. Mov Disord 2005;20:1633–1636.
9. Kim J, Hong S, Kim GP, et al. Importance of low-range CAG expansion and CAA interruption in SCA2 parkinsonism. Arch Neurol 2007;64:1510–1518.
10. Moretti P, Blazo M, Garcia L, et al. Spinocerebellar ataxia type 2 (SCA2) presenting with ophthalmoplegia and developmental delay in infancy. Am J Med Genet A 2004; 124A:392–396.
11. Abdel-Aleem A, Zaki MS. Spinocerebellar ataxia type 2 (SCA2) in an Egyptian family presenting with polyphagia and marked CAG expansion in infancy. J Neurol 2008; 255:413–419.
12. Dirik E, Yiş U, Başak N, Soydan E, Hüdaoğlu O, Ozgönül F. Spinocerebellar ataxia type 2 in a Turkish family. J Child Neurol 2007;22:891–894.
13. Ramocki MB, Chapieski L, McDonald RO, Fernandez F, Malphrus AD. Spinocerebellar ataxia type 2 presenting with cognitive regression in childhood. J Child Neurol 2008;23:999–1001.
14. Pulst S, Santos N, Wang D, et al. Spinocerebellar ataxia type 2: polyQ repeat variation in the CACNA1A calcium channel modifies age of onset. Brain 2005;128:2297–2303.
15. Huynh DP, Yang H, Vakharia H, Nguyen D, Pulst SM. Expansion of the polyQ repeat in ataxin-2 alters its Golgi localization, disrupts the Golgi complex and causes cell death. Hum Mol Genet 2003;12:1485–1496.
16. Nonhoff U, Ralser M, Welzel F, et al. Ataxin-2 interacts with the DEAD/H-box RNA helicase DDX6 and interferes with P-bodies and stress granules. Mol Biol Cell 2007;18:1385–1396.
17. Liu J, Tang T, Tu H, et al. Deranged calcium signaling and neurodegeneration in spinocerebellar ataxia type 2. J Neurosci 2009;29:9148–9162.
18. Lim J, Hao T, Shaw C, et al. A protein-protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell 2006;125:801–814.
19. Huynh DP, Figueroa K, Hoang N, Pulst SM. Nuclear localization or inclusion body formation of ataxin-2 are not necessary for SCA2 pathogenesis in mouse or human. Nat Genet 2000;26:44–50.
20. Huynh DP, Maalouf M, Silva AJ, Schweizer FE, Pulst SM. Dissociated fear and spatial learning in mice with deficiency of ataxin-2. PLoS ONE 2009;4:e6235.
21. Babovic-Vuksanovic D, Snow K, Patterson MC, Michels VV. Spinocerebellar ataxia type 2 (SCA 2) in an infant with extreme CAG repeat expansion. Am J Med Genet 1998;79:383–387.
22. Shibata H, Huynh DP, Pulst SM. A novel protein with RNA-binding motifs interacts with ataxin-2. Hum Mol Genet 2000;9:1303–1313.
23. Bhalla K, Phillips HA, Crawford J, et al. The de novo chromosome 16 translocations of two patients with abnormal phenotypes (mental retardation and epilepsy) disrupt the A2BP1 gene. J Hum Genet 2004;49:308–311.
24. Martin CL, Duvall JA, Ilkin Y, et al. Cytogenetic and molecular characterization of A2BP1/FOX1 as a candidate gene for autism. Am J Med Genet B Neuropsychiatr Genet 2007;144B:869–876.
25. Gomez CM, Thompson RM, Gammack JT, et al. Spinocerebellar ataxia type 6: gaze-evoked and vertical nystagmus, Purkinje cell degeneration, and variable age of onset. Ann Neurol 1997;42:933–950.
26. Lastres-Becker I, Rüb U, Auburger G. Spinocerebellar ataxia 2 (SCA2). Cerebellum 2008;7:115–124.
27. Robison AJ, Bass MA, Jiao Y, et al. Multivalent interactions of calcium/calmodulin-dependent protein kinase II with the postsynaptic density proteins NR2B, densin-180, and alpha-actinin-2. J Biol Chem 2005;280:35329–35336.
28. Deng F, Price MG, Davis CF, Mori M, Burgess DL. Stargazin and other transmembrane AMPA receptor regulating proteins interact with synaptic scaffolding protein MAGI-2 in brain. J Neurosci 2006;26:7875–7884.
29. Saitsu H, Tohyama J, Kumada T, et al. Dominant-negative mutations in alpha-II spectrin cause West syndrome with severe cerebral hypomyelination, spastic quadriplegia, and developmental delay. Am J Hum Genet 2010;86:881–891.
30. Van Epps HA, Hayashi M, Lucast L, et al. The zebrafish nrc mutant reveals a role for the polyphosphoinositide phosphatase synaptojanin 1 in cone photoreceptor ribbon anchoring. J Neurosci 2004;24:8641–8650.
31. Holzhausen LC, Lewis AA, Cheong KK, Brockerhoff SE. Differential role for synaptojanin 1 in rod and cone photoreceptors. J Comp Neurol 2009;517:633–644.
32. Saitsu H, Kato M, Mizuguchi T, et al. De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. Nat Genet 2008;40: 782–788.
33. Marshall CR, Young EJ, Pani AM, et al. Infantile spasms is associated with deletion of the MAGI2 gene on chromosome 7q11.23-q21.11. Am J Hum Genet 2008;3:106–111.
34. Ding Y, Zhang Y, He B, Yue W, Zhang D, Zou L. A possible association of responsiveness to adrenocorticotropic hormone with specific GRIN1 haplotypes in infantile spasms. Dev Med Child Neurol 2010;2:1028–1032.
35. Endele S, Rosenberger G, Geider K, et al. Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet 2010;2:1021–1026.
36. Gong L, De Camilli P. Regulation of postsynaptic AMPA responses by synaptojanin 1. Proc Natl Acad Sci USA 2008;05:17561–17566.
37. Huichalaf C, Sakai K, Jin B, et al. Expansion of CUG RNA repeats causes stress and inhibition of translation in myotonic dystrophy 1 (DM1) cells. FASEB J 2010;4: 3706–3719.
38. Lee JE, Cooper TA. Pathogenic mechanisms of myotonic dystrophy. Biochem Soc Trans 2009;7:1281–1286.