Date of Search: Dec 2016

The proposed new list of autosomal dominantly inherited ataxias

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| New designation | Less common movement phenotype | Clinical clues | Inheritance | Locus symbol |
| **Pure or relatively pure ataxia** |
| ATX-*SPTBN2 [1]* |  | Pure ataxiaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 600224 | AD | SCA5 |
| ATX-*CACNA1A [2]* |  | Pure ataxia. Allelic with episodic ataxia type 2 and familial hemiplegic migraine type 1.GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1140/OMIM 183086 | AD | SCA6 |
| ATX-*TTBK2 [3]* |  | Pure ataxiaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1757/OMIM 604432 | AD | SCA11 |
| ATX-*PDYN [4]* |  | Pure ataxiaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 610245 | AD | SCA23 |
| ATX-*ATXN8OS [5]* |  | Relatively pure; pyramidal signs, neuropsychiatric featuresGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1268/OMIM 608768 | AD | SCA8 |
| ATX-*PPP2R2B [6]* |  | Relatively pure; head and hand tremorGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1202/OMIM 604326 | AD | SCA12 |
| ATX-*PRKCG [7]* |  | Relatively pure; sometimes other movement disorders (dystonia, myoclonus) GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1399/OMIM 605361 | AD | SCA14 |
| ATX-*ITPR1 [8]*, [9] |  | Relatively pure; myoclonus, dystoniaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1362/OMIM 606658 | AD | SCA15/16 |
| ATX-KCND3 [10] |  | Relatively pure; hand tremor, peripheral neuropathy, cognitive disturbancesGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 607346 | AD | SCA19/22 |
| ATX-*FGF14 [11]* |  | Relatively pure; early-onset hand tremor, orofacial dyskinesia, behavioural problemsGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 609307 | AD | SCA27 |
| ATX-*TGM6 [12]* |  | Relatively pure; pyramidal features, cervical dystoniaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 613908 | AD | SCA35 |
| ATX-*ELOVL5 [13]* |  | Relatively pure; neuropathyGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 615957 | AD | SCA38 |
| ATX-CACNA1G [14] |  | Pyramidal features; facial myokymiahttp://omim.org/entry/604065 | AD | SCA42 |
| ATX-ELOVL4[15] |  | Relatively pure; peripheral neuropathyErythrokeratodermiahttp://omim.org/entry/133190 | AD | SCA34 |
| **Complex Ataxia (ataxias that can often have other neurological features)** |
| ATX-*ATXN1[3]* |  | Marked non-ataxia features; can have dominant choreapyramidal features, peripheral neuropathy, ophthalmoplegiaGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1184/OMIM 164400 | AD | SCA1 |
| ATX-*ATXN2 [16]* | Parkinsonism [17] | Marked non-ataxia features, can have predominant parkinsonism or chorea; neuronopathy, dementia, myoclonusGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1275/OMIM 183090 | AD | SCA2 |
| ATX-*ATXN3 [18]* | HSP, dystonia [19], [20] | Marked non-ataxia features; can have predominant parkinsonism, dystonia, chorea, spasticity, neuropathy, lower motor neuron involvementGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1196/OMIM 109150 | AD | SCA3 |
| ATX-*ATXN7 [21]* |  | Retinitis pigmentosa with marked visual loss GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1256/OMIM 164500 | AD | SCA7 |
| ATX-*ATXN10 [22]* |  | SeizuresGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1175/OMIM 603516 | AD | SCA10 |
| ATX-*TBP [23]* | Chorea [24] | Marked non-ataxia features, can present with predominant chorea. May be HD-likeGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1438/OMIM 607136 | AD | SCA17, HDL4 |
| ATX-*TMEM240 [25]* |  | Cognitive impairment / mental retardationGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 607454 | AD | SCA21 |
| ATX-*AFG3L2 [26]* |  | OphthalmoparesisGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK54582/OMIM 610246 | AD | SCA28 |
| ATX-*BEAN1 [27]* |  | Hearing loss, vertigoGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 117210 | AD | SCA31 |
| ATX-*NOP56 [28]* |  | Motor neuron involvementGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK231880/OMIM 614153 | AD | SCA36 |
| ATX-*DNMT1 [29]* |  | Sensorineural deafness, narcolepsy, dementiaGeneReviews http://www.ncbi.nlm.nih.gov/books/NBK84112/OMIM: 126375 | AD | None |
| ATX-*ATN1 [30]* | Chorea [31] | Dentatorubropallidoluysian atrophy (DRPLA): Myoclonus, chorea, parkinsonism, dementia, supranuclear gaze palsy, seizures (particularly in young patients)GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1491/OMIM: 607462 | AD | None |
| ATX/HSP-*VAMP1 [32]* |  | Spastic ataxia, supranuclear upgaze limitationGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1138/OMIM 108600 | AD | SPAX1 |
| **Disorders that usually present with other phenotypes but can have predominant ataxia** |
| *GFAP [33]* | Spastic ataxia [34] | Usually presenting with infantile onset megalencephaly, (pseudo)bulbar signs, spasticity, cognitive deficits, developmental delay, white matter changes (Alexander disease)GeneReviews<http://www.ncbi.nlm.nih.gov/books/NBK1172/>OMIM 137780 | AD |  |
| HSP-*KIF1C [35]*Allelic with autosomal recessive spastic ataxia at the SAX2 locus. | Dystonia, ataxia [35] | Pure and complicated, chorea, myoclonus, dysarthria, developmental delay, mild mental retardation, hypodontia, ptosis, short stature, sensorineural deafness, pes planus, white matter lesions.GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1509/OMIM 611302 | AR | SPG58 |
| HSP/NBIA-*FA2H [36]* | Dystonia, Ataxia [37]  | Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN) Dystonia, ataxiaIron accumulation: GP (more subtle than other NBIAs)Additional clinical features: Spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizuresGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1509/OMIM 612319 | AR | SPG35 |
| HSP-*REEP1 [38]* | Ataxia [39] | Pure or complex; distal motor neuronopathy, axonal Peripheral neuropathy, Silver-like syndrome, cerebellar ataxia, tremor, dementia.GeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1509/OMIM 610250 | AD | SPG31 |
| NBIA/DYT/PARK\*-*PLA2G6 [40]* | Ataxia [41] | *PLA2G6*-associated neurodegeneration (PLAN):Dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood phenotype)Iron accumulation: GP, SN in some; adults may have striatal involvement; about half of INAD and the majority of adult-onset cases lack brain iron accumulation on MRIGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1675/OMIM 612953 | AR | NBIA2, PARK14 |
| HSP/NBIA- *FA2H [36]* |  Dystonia, parkinsonism, ataxia [37]  | Fatty Acid Hydroxylase-associated Neurodegeneration (FAHN) [37]:Iron accumulation: GP (more subtle than other NBIAs)Additional clinical features: Spastic tetraparesis, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizuresGeneReviewshttp://www.ncbi.nlm.nih.gov/books/NBK1509/OMIM 612319 | AR | SPG35 |

AD: autosomal dominant; CPEO: chronic progressive external ophthalmoplegia

\* Mutations in this gene more commonly cause infantile neuroaxonal dystrophy (INAD): Developmental delay / regression, hypotonia, spasticity / pyramidal signs, optic nerve atrophy, sensorimotor neuropathy, seizures

1. Ikeda, Y., et al., *Spectrin mutations cause spinocerebellar ataxia type 5.* Nat Genet, 2006. **38**(2): p. 184-90.

2. Zhuchenko, O., et al., *Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel.* Nat Genet, 1997. **15**(1): p. 62-9.

3. Banfi, S., et al., *Identification and characterization of the gene causing type 1 spinocerebellar ataxia.* Nat Genet, 1994. **7**(4): p. 513-20.

4. Bakalkin, G., et al., *Prodynorphin mutations cause the neurodegenerative disorder spinocerebellar ataxia type 23.* Am J Hum Genet, 2010. **87**(5): p. 593-603.

5. Koob, M.D., et al., *An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8).* Nat Genet, 1999. **21**(4): p. 379-84.

6. Holmes, S.E., et al., *Expansion of a novel CAG trinucleotide repeat in the 5' region of PPP2R2B is associated with SCA12.* Nat Genet, 1999. **23**(4): p. 391-2.

7. Chen, D.H., et al., *Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant nonepisodic cerebellar ataxia.* Am J Hum Genet, 2003. **72**(4): p. 839-49.

8. Iwaki, A., et al., *Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16.* J Med Genet, 2008. **45**(1): p. 32-5.

9. van de Leemput, J., et al., *Deletion at ITPR1 underlies ataxia in mice and spinocerebellar ataxia 15 in humans.* PLoS Genet, 2007. **3**(6): p. e108.

10. Lee, Y.C., et al., *Mutations in KCND3 cause spinocerebellar ataxia type 22.* Ann Neurol, 2012. **72**(6): p. 859-69.

11. van Swieten, J.C., et al., *A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia [corrected].* Am J Hum Genet, 2003. **72**(1): p. 191-9.

12. Wang, J.L., et al., *TGM6 identified as a novel causative gene of spinocerebellar ataxias using exome sequencing.* Brain, 2010. **133**(Pt 12): p. 3510-8.

13. Di Gregorio, E., et al., *ELOVL5 mutations cause spinocerebellar ataxia 38.* American Journal of Human Genetics, 2014. **95**(2): p. 209-17.

14. Coutelier, M., et al., *A Recurrent Mutation in CACNA1G Alters Cav3.1 T-Type Calcium-Channel Conduction and Causes Autosomal-Dominant Cerebellar Ataxia.* Am J Hum Genet, 2015. **97**(5): p. 726-37.

15. Morino, H., et al., *A mutation in the low voltage-gated calcium channel CACNA1G alters the physiological properties of the channel, causing spinocerebellar ataxia.* Mol Brain, 2015. **8**: p. 89.

16. Pulst, S.M., et al., *Moderate expansion of a normally biallelic trinucleotide repeat in spinocerebellar ataxia type 2.* Nat Genet, 1996. **14**(3): p. 269-76.

17. Shan, D.E., et al., *Spinocerebellar ataxia type 2 presenting as familial levodopa-responsive parkinsonism.* Ann Neurol, 2001. **50**(6): p. 812-5.

18. Kawaguchi, Y., et al., *CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1.* Nat Genet, 1994. **8**(3): p. 221-8.

19. Munchau, A., et al., *Machado-Joseph disease presenting as severe generalised dystonia in a German patient.* J Neurol, 1999. **246**(9): p. 840-2.

20. Song, Y., et al., *Spinocerebellar ataxia type 3/Machado-Joseph disease manifested as spastic paraplegia: A clinical and genetic study.* Exp Ther Med, 2015. **9**(2): p. 417-420.

21. Trottier, Y., et al., *Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias.* Nature, 1995. **378**(6555): p. 403-6.

22. Matsuura, T., et al., *Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10.* Nat Genet, 2000. **26**(2): p. 191-4.

23. Koide, R., et al., *A neurological disease caused by an expanded CAG trinucleotide repeat in the TATA-binding protein gene: a new polyglutamine disease?* Hum Mol Genet, 1999. **8**(11): p. 2047-53.

24. Schneider, S.A., et al., *Phenotypic homogeneity of the Huntington disease-like presentation in a SCA17 family.* Neurology, 2006. **67**(9): p. 1701-3.

25. Delplanque, J., et al., *TMEM240 mutations cause spinocerebellar ataxia 21 with mental retardation and severe cognitive impairment.* Brain, 2014. **137**(Pt 10): p. 2657-63.

26. Di Bella, D., et al., *Mutations in the mitochondrial protease gene AFG3L2 cause dominant hereditary ataxia SCA28.* Nat Genet, 2010. **42**(4): p. 313-21.

27. Sato, N., et al., *Spinocerebellar ataxia type 31 is associated with "inserted" penta-nucleotide repeats containing (TGGAA)n.* Am J Hum Genet, 2009. **85**(5): p. 544-57.

28. Kobayashi, H., et al., *Expansion of intronic GGCCTG hexanucleotide repeat in NOP56 causes SCA36, a type of spinocerebellar ataxia accompanied by motor neuron involvement.* Am J Hum Genet, 2011. **89**(1): p. 121-30.

29. Winkelmann, J., et al., *Mutations in DNMT1 cause autosomal dominant cerebellar ataxia, deafness and narcolepsy.* Hum Mol Genet, 2012. **21**(10): p. 2205-10.

30. Koide, R., et al., *Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA).* Nat Genet, 1994. **6**(1): p. 9-13.

31. Nørremølle, A., et al., *Elongated CAG repeats of the B37 gene in a Danish family with dentato-rubro-pallido-luysian atrophy.* Human Genetics, 1995. **95**(3): p. 313-318.

32. Bourassa, C.V., et al., *VAMP1 mutation causes dominant hereditary spastic ataxia in Newfoundland families.* Am J Hum Genet, 2012. **91**(3): p. 548-52.

33. Brenner, M., et al., *Mutations in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease.* Nat Genet, 2001. **27**(1): p. 117-20.

34. Kaneko, H., et al., *Novel GFAP mutation in patient with adult-onset Alexander disease presenting with spastic ataxia.* Movement Disorders, 2009. **24**(9): p. 1393-1395.

35. Dor, T., et al., *KIF1C mutations in two families with hereditary spastic paraparesis and cerebellar dysfunction.* J Med Genet, 2014. **51**(2): p. 137-42.

36. Edvardson, S., et al., *Mutations in the fatty acid 2-hydroxylase gene are associated with leukodystrophy with spastic paraparesis and dystonia.* Am J Hum Genet, 2008. **83**(5): p. 643-8.

37. Kruer, M.C., et al., *Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA).* Annals of Neurology, 2010. **68**(5): p. 611-618.

38. Zuchner, S., et al., *Mutations in the novel mitochondrial protein REEP1 cause hereditary spastic paraplegia type 31.* Am J Hum Genet, 2006. **79**(2): p. 365-9.

39. Goizet, C., et al., *REEP1 mutations in SPG31: frequency, mutational spectrum, and potential association with mitochondrial morpho-functional dysfunction.* Hum Mutat, 2011. **32**(10): p. 1118-27.

40. Paisan-Ruiz, C., et al., *Characterization of PLA2G6 as a locus for dystonia-parkinsonism.* Ann Neurol, 2009. **65**(1): p. 19-23.

41. Illingworth, M.A., et al., *PLA2G6-associated neurodegeneration (PLAN): Further expansion of the clinical, radiological and mutation spectrum associated with infantile and atypical childhood-onset disease.* Molecular Genetics and Metabolism, 2014. **112**(2): p. 183-189.