Date of search: Aug 2020

Recently identified or confirmed forms of hereditary myoclonus

New designation	Less common movement phenotype	Disease entity and clinical features	OMIM	MOI
Prominent myoclonus syndromes				
MYC-*DHDDS*[1, 2]	ataxia, dystonia, tremor	Developmental delay and seizures with or without movement abnormalities (DEDSM); global developmental delay, variable ID, early-onset seizures, and myoclonic component (can be prominent)	617836	AD
MYC-*GRIA3*[3-5]	Chorea[*]	Syndromic intellectual disability disorder (MRXSW); broad phenotypic spectrum including mental retardation and seizures, myoclonus, and variable motor and behavioral impairment	300699	XLR
MYC-*MFSD8*[6, 7]		Neuronal ceroid lipofuscinosis 7 (CLN7); neurodegenerative disease with variable phenotypic features including seizures, myoclonus, mental regression, speech impairment, loss of vision, and personality disorder	610951	AR
MYC- *SEMA6B*[8-12]		Progressive myoclonic epilepsy-11 (EPM11); neurodegenerative disease with infancy-onset of developmental regression and seizures, followed by additional neurological symptoms, e.g., spasticity, loss of independent ambulation, myoclonus, tremor, ataxia, and severe cognitive impairment in the first and second decade	618876	AD
MYC/PxMD-*SCN8A*[A,13-15]	Ataxia	Familial myoclonus with childhood-onset of isolated action-induced nonepileptic myoclonus affecting the upper limbs, nonprogressive; also epilepsy or developmental and epileptic encephalopathy phenotypes	618364	AD
Combined phenotypes: where myoclonus coexists with another movement disorder as a prominent consistent feature				
MYC/DYT-*KCTD17*[16-19]		Onset of mild myoclonic symptoms in the first or second decade of life, followed by later onset of progressive dystonia with predominant involvement of the cranial and laryngeal muscles; dystonia dominates the clinical picture	616398	AD
ATX/MYC-*NUS1*[1, 12]	Tremor, parkinsonism, dystonia[20, 21]	Mental retardation 55 with seizures (MRD55); broad phenotypic spectrum including developmental delay, intellectual disability, ataxia, myoclonus, (myoclonic) seizures, resting and intention tremor, and rarely parkinsonism	617831	AD
Disorders that usually present with other phenotypes but can have dominant myoclonus				
Gene	**Disease**	**OMIM**	**Clinical phenotype and comment**	**MOI**

ATX/PxMD-*CACNA1A*[B, 22, 23]	Episodic ataxia type 2 (EA2)	108500	Gene linked to EA2, but recent publications report phenotypes including progressive myoclonus epilepsy	AD
ATX-*MT-ATP6*[24, 25]	See table 3 (ATX list)	551500	Variable phenotype predominantly including ataxia in the majority, but also myoclonus in a minority, for details see table 3	mt
EEF1A2[26-28]	Developmental and epileptic encephalopathy 33 (DEE33), Mental retardation (MRD38)	616409, 616393	Epilepsy phenotype with various types of seizures in the first month of life and severe global developmental delay with impaired intellectual development and poor or absent speech, sometimes prominent myoclonic epilepsy	AD
RORB[29, 30]	Susceptibility to idiopathic generalized epilepsy 15 (EIG15)	618357	Epilepsy phenotype with various types of seizures in the first decade (most commonly absence seizures), majority with developmental delay with impaired intellectual development, predominant eyelid myoclonus	AD
SCN2A[31-34]	Developmental and epileptic encephalopathy 11 (DEE11), Episodic ataxia type 9 (EA9), Benign familial infantile seizures 3	613721, 618924, 607745	Gene linked to multiple diseases and therefore with a broad and overlapping phenotypic spectrum including developmental delay, seizures and various movement disorders, myoclonus can be a dominant feature	AD
SETD1B[35]	Intellectual developmental disorder with seizures and language delay	619000	Global developmental delay with speech and language impairment and seizures, mostly myoclonic (absence) seizures as predominant feature, often accompanying behavioral abnormalities (autism spectrum disorder or anxiety), sometimes additional features like facial dysmorphism, tapering fingers, and pigmentary skin changes	AD

AD = autosomal dominant, AR = autosomal recessive, DD = developmental delay, ID = intellectual disability, MOI = mode of inheritance, OMIM = Online Mendelian Inheritance in Man (https://www.omim.org/about), XLD = x-linked dominant, XLR = x-linked recessive

* Chorea is rather equally prominent in respective cases, but this finding needs to be independently confirmed. This gene is currently in the list of unconfirmed candidate genes of hereditary chorea (Supplementary table 5).

A Mutations in this gene can also cause autosomal-dominant cognitive impairment with or without cerebellar ataxia (OMIM 614306), autosomal-dominant developmental and epileptic encephalopathy 13 (DEE13, OMIM 614558), and/or autosomal-dominant benign familial infantile seizures type 5 (OMIM 617080).

B Mutations in this gene can also cause autosomal-dominant Spinocerebellar ataxia type 6 (OMIM 183086), autosomal-dominant familial hemiplegic migraine with or without progressive cerebellar ataxia (OMIM 141500), and/or autosomal-dominant developmental and epileptic encephalopathy type 41 (OMIM 617106).[36]

References

1. Hamdan FF, Myers CT, Cossette P, et al. High Rate of Recurrent De Novo Mutations in Developmental and Epileptic Encephalopathies. Am J Hum Genet 2017;101(5):664-685.

2. Togashi N, Fujita A, Shibuya M, et al. Fifteen-year follow-up of a patient with a DHDDS variant with non-progressive early onset myoclonic tremor and rare generalized epilepsy. Brain Dev 2020;42(9):696-699.

3. Wu Y, Arai AC, Rumbaugh G, et al. Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. Proc Natl Acad Sci U S A 2007;104(46):18163-18168.

4. Piard J, Bereau M, XiangWei W, et al. The GRIA3 c.2477G > A Variant Causes an Exaggerated Startle Reflex, Chorea, and Multifocal Myoclonus. Mov Disord 2020;35(7):1224-1232.

5. Trivisano M, Santarone ME, Micalizzi A, et al. GRIA3 missense mutation is cause of an x-linked developmental and epileptic encephalopathy. Seizure 2020;82:1-6.

6. Patino LC, Battu R, Ortega-Recalde O, et al. Exome sequencing is an efficient tool for variant late-infantile neuronal ceroid lipofuscinosis molecular diagnosis. PLoS One 2014;9(10):e109576.

7. Kozina AA, Okuneva EG, Baryshnikova NV, et al. A novel MFSD8 mutation in a Russian patient with neuronal ceroid lipofuscinosis type 7: a case report. BMC Med Genet 2018;19(1):151.

8. Hamanaka K, Imagawa E, Koshimizu E, et al. De Novo Truncating Variants in the Last Exon of SEMA6B Cause Progressive Myoclonic Epilepsy. Am J Hum Genet 2020;106(4):549-558.

9. Herzog R, Hellenbroich Y, Bruggemann N, et al. Zonisamide-responsive myoclonus in SEMA6B-associated progressive myoclonic epilepsy. Ann Clin Transl Neurol 2021;8(7):1524-1527.

10. Li Q, Liu M, Huang DP, et al. A De Novo SEMA6B Variant in a Chinese Patient with Progressive Myoclonic Epilepsy-11 and Review of the Literature. J Mol Neurosci 2021;71(9):1944-1950.

11. Xiaozhen S, Fan Y, Fang Y, et al. Novel Truncating and Missense Variants in SEMA6B in Patients With Early-Onset Epilepsy. Front Cell Dev Biol 2021;9:633819.

12. Courage C, Oliver KL, Park EJ, et al. Progressive myoclonus epilepsies-Residual unsolved cases have marked genetic heterogeneity including dolichol-dependent protein glycosylation pathway genes. Am J Hum Genet 2021;108(4):722-738.

13. Wagnon JL, Mencacci NE, Barker BS, et al. Partial loss-of-function of sodium channel SCN8A in familial isolated myoclonus. Hum Mutat 2018;39(7):965-969.

14. Gardella E, Marini C, Trivisano M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology 2018;91(12):e1112-e1124.

15. Denis J, Villeneuve N, Cacciagli P, et al. Clinical study of 19 patients with SCN8A-related epilepsy: Two modes of onset regarding EEG and seizures. Epilepsia 2019;60(5):845-856.

16. Mencacci NE, Rubio-Agusti I, Zdebik A, et al. A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia. Am J Hum Genet 2015;96(6):938-947.

17. Marce-Grau A, Correa M, Vanegas MI, et al. Childhood onset progressive myoclonic dystonia due to a de novo KCTD17 splicing mutation. Parkinsonism Relat Disord 2019;61:7-9.

18. Graziola F, Stregapede F, Travaglini L, et al. A novel KCTD17 mutation is associated with childhood early-onset hyperkinetic movement disorder. Parkinsonism Relat Disord 2019;61:4-6.

19. Todisco M, Gana S, Cosentino G, et al. KCTD17-related myoclonus-dystonia syndrome: clinical and electrophysiological findings of a patient with atypical late onset. Parkinsonism Relat Disord 2020;78:129-133.

20. Wirth T, Tranchant C, Drouot N, et al. Increased diagnostic yield in complex dystonia through exome sequencing. Parkinsonism Relat Disord 2020;74:50-56.

21. Gunzler SA, DeBrosse SD. Generalized Dystonia as a Prominent Feature in a Case of NUS1 Gene Mutation. Can J Neurol Sci 2021;48(3):433-434.

22. Hayashida T, Saito Y, Ishii A, et al. CACNA1A-related early-onset encephalopathy with myoclonic epilepsy: A case report. Brain Dev 2018;40(2):130-133.

23. Lv Y, Wang Z, Liu C, Cui L. Identification of a novel CACNA1A mutation in a Chinese family with autosomal recessive progressive myoclonic epilepsy. Neuropsychiatr Dis Treat 2017;13:2631-2636.

24. Mordel P, Schaeffer S, Dupas Q, et al. A 2 bp deletion in the mitochondrial ATP 6 gene responsible for the NARP (neuropathy, ataxia, and retinitis pigmentosa) syndrome. Biochem Biophys Res Commun 2017;494(1-2):133-137.

25. Bugiardini E, Bottani E, Marchet S, et al. Expanding the molecular and phenotypic spectrum of truncating MT-ATP6 mutations. Neurol Genet 2020;6(1):e381.

26. Inui T, Kobayashi S, Ashikari Y, et al. Two cases of early-onset myoclonic seizures with continuous parietal delta activity caused by EEF1A2 mutations. Brain Dev 2016;38(5):520-524.

27. Lam WW, Millichap JJ, Soares DC, et al. Novel de novo EEF1A2 missense mutations causing epilepsy and intellectual disability. Mol Genet Genomic Med 2016;4(4):465-474.

28. De Rinaldis M, Giorda R, Trabacca A. Mild epileptic phenotype associates with de novo eef1a2 mutation: Case report and review. Brain Dev 2020;42(1):77-82.

29. Rudolf G, Lesca G, Mehrjouy MM, et al. Loss of function of the retinoid-related nuclear receptor (RORB) gene and epilepsy. Eur J Hum Genet 2016;24(12):1761-1770.

30. Sadleir LG, de Valles-Ibanez G, King C, et al. Inherited RORB pathogenic variants: Overlap of photosensitive genetic generalized and occipital lobe epilepsy. Epilepsia 2020;61(4):e23-e29.

31. Liao Y, Anttonen AK, Liukkonen E, et al. SCN2A mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. Neurology 2010;75(16):1454-1458.

32. Huang Q, Yu L, Ma M, Qi H, Wu Y. Novel SCN2A mutation in a family associated with juvenile-onset myoclonus: Case report. Medicine (Baltimore) 2019;98(8):e14698.

33. Lee S, Kim SH, Kim B, et al. Genetic diagnosis and clinical characteristics by etiological classification in early-onset epileptic encephalopathy with burst suppression pattern. Epilepsy Res 2020;163:106323.

34. Tang S, Addis L, Smith A, et al. Phenotypic and genetic spectrum of epilepsy with myoclonic atonic seizures. Epilepsia 2020;61(5):995-1007.

35. Hiraide T, Hattori A, Ieda D, et al. De novo variants in SETD1B cause intellectual disability, autism spectrum disorder, and epilepsy with myoclonic absences. Epilepsia Open 2019;4(3):476-481.

36. Indelicato E, Boesch S. From Genotype to Phenotype: Expanding the Clinical Spectrum of CACNA1A Variants in the Era of Next Generation Sequencing. Front Neurol 2021;12:639994.