Curr Neurol Neurosci Rep (2017) 17: 97
https://doi.org/10.1007/s11910-017-0806-2

GENETICS (V BONIFATI, SECTION EDITOR)

Emerging Monogenic Complex Hyperkinetic Disorders

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Published online: 30 October 2017

Abstract
Purpose of Review Hyperkinetic movement disorders can manifest alone or as part of complex phenotypes. In the era of next-generation sequencing (NGS), the list of monogenic complex movement disorders is rapidly growing. This review will explore the main features of these newly identified conditions.
Recent Findings Mutations in *ADCY5* and *PDE10A* have been identified as important causes of childhood-onset dyskinesias and *KMT2B* mutations as one of the most frequent causes of complex dystonia in children. The delineation of the phenotypic spectrum associated with mutations in *ATP1A3*, *FOXG1*, *GNAO1*, *GRIN1*, *FRRS1L*, and *TBC1D24* is revealing an expanding genetic overlap between epileptic encephalopathies, developmental delay/intellectual disability, and hyperkinetic movement disorders,.
Summary Thanks to NGS, the etiology of several complex hyperkinetic movement disorders has been elucidated. Importantly, NGS is changing the way clinicians diagnose these complex conditions. Shared molecular pathways, involved in early stages of brain development and normal synaptic transmission, underlie basal ganglia dysfunction, epilepsy, and other neurodevelopmental disorders.

Keywords Hyperkinetic · Movement disorders · Genetics · Next-generation sequencing · Epilepsy

This article is part of the Topical Collection on *Genetics*

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Introduction

Hyperkinetic movement disorders are a heterogeneous group of neurological disorders defined by an excess of involuntary movement production.

Based on the clinical phenomenology, hyperkinetic movement disorders are classified in different clinical entities, including among others dystonia, chorea, and myoclonus. Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, and patterned movements and/or postures. Chorea features continuous and brief involuntary movements, typically flowing from one body part to another in an unpredictable fashion in terms of timing, speed, and direction. Myoclonus defines shock-like involuntary jerks caused by rapid muscle contractions [1].

The etiology of these disorders is often genetically determined, especially in pediatric cases, and mutations in a rapidly growing number of genes have been causally linked to hyperkinetic movement disorders.

Traditionally, a detailed characterization of the predominant movement disorder observed on examination would lay the bases for subsequent investigations, including targeted genetic analysis of mutations in genes that are known to be associated with a specific movement disorder.

However, there are several pitfalls that can make establishing a precise diagnosis on clinical grounds a true challenge. First, multiple hyperkinetic movement disorders are frequently observed together in the same patient with a considerable degree of overlap, which makes defining the predominant type of movement disorder very difficult. Second, the clinical presentation of hyperkinetic movement disorders is often complex and highly variable, which may lead different neurologists to label differently the same movement disorder. Finally, additional neurological features (including intellectual disability (ID), epilepsy, spasticity, ataxia, and structural abnormalities of the brain) are often observed, in variable combinations, especially in cases with pediatric onset.

Hence, it is not surprising how the diagnostic work-up for complex hyperkinetic movement disorders may easily turn into long and painful diagnostic odysseys for patients and their families.

Importantly, the advent of next-generation sequencing (NGS) is rapidly changing the way clinicians diagnose and identify these conditions. Diagnostic approaches based on NGS technologies (i.e., targeted gene sequencing panels or whole-exome sequencing) are progressively becoming a first-line asset in the diagnostic pipeline for these complex disorders, partially bypassing the difficulties of the clinical assessment.

To increase awareness of these individually rare conditions, in this review, we will summarize the main clinical and genetic features of the genetically determined complex hyperkinetic movement disorders identified in the last 5 years (summarized in Table 1).

Complex Hyperkinetic Movement Disorders Without Epilepsy as Core Feature

ADCY5-Related Disorders

The first pathogenic dominant mutation in *ADCY5* was identified in a large kindred of German descent initially described in 2001 by Fernandez et al. [2•, 3]. Affected subjects showed an early-onset hyperkinetic movement disorder initially named familial dyskinesia with facial myokimia (FDFM). Subsequently, mutations in this gene were found in patients with childhood-onset chorea and dystonia, as well as in patients with a non-progressive condition resembling benign hereditary chorea (BHC) who tested negative for *NKX2-1* mutations [4, 5•]. So far, 70 genetically confirmed cases belonging to 45 different families have been reported [2–4, 5•, 6••, 7–14, 15•, 16]. Since the first description, the phenotype associated to *ADCY5* mutations has largely broadened and consequently, the original term FDFM has been replaced by a more comprehensive definition (*ADCY5*-related dyskinesias). Patients present virtually in all cases with axial hypotonia and delayed motor and/or language milestones during infancy, associated with early-onset chorea with a generalized distribution, classically involving also the facial muscles and the perioral region [5•, 15•]. Dystonic posturing of the limbs and myoclonic jerks can be prominent, mimicking a myoclonus-dystonia-like phenotype but without the classical upper body distribution observed in *SGCE* mutation carriers [15•, 17]. Episodic exacerbations of movement disorder lasting up to hours have been described in most *ADCY5*-positive cases, being frequently not only related to sleep but also triggered by febrile illnesses and other various stressors [18]. Such episodes can precede the onset of the chronic movement disorder that eventually dominate patients' clinical picture [15•]. Pyramidal signs in the lower limbs and dysarthria are common clinical findings; in single kindred, dilated cardiomyopathy was reported to cosegregate with *ADCY5* mutations in affected individuals, but this finding has never been observed in other families [3]. Both dominant families and sporadic cases due to de novo mutations have been published, with a recurrent missense mutation (p.Arg418Trp) reported in the majority the affected cases. Two additional mutations at amino acidic residue 418 (p.Arg418Gln and p.Arg418Gly) have been subsequently reported, thus indicating that arginine 418 is a mutational hot spot with a relevant pathogenetic role [6••, 8]. The severity of the movement disorder and the consequent degree of functional disability are variable in affected subjects. The available evidence suggests that the p.Arg418Trp mutation is responsible for a more severe clinical picture, whereas the p.Ala726Thr mutation is associated with a milder phenotype [6••, 15•]. Besides genotype-phenotype correlation, somatic mosaicism detected in some mildly affected patients further explains the clinical heterogeneity of *ADCY5* mutated subjects [5•, 6••].

In terms of therapy, anticholinergics, benzodiazepines (clonazepam), tetrabenazine, baclofen, neuroleptics, and anticonvulsants alone or in combination have been administered to reduce dyskinesias, with variable response; acetazolamide, a carbonic anhydrase inhibitor, has been successfully used in two patients [2•]. Deep brain stimulation (DBS) of bilateral globus pallidus interna (GPi) has been performed in four patients, with moderate improvement of chorea [9, 11].

From a disease mechanism point of view, *ADCY5* encodes adenyl cyclase 5 (AC5), an enzyme most abundantly expressed in striatal neurons that converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP). Importantly, dopamine and adenosine modulation of striatal medium spiny neurons (MSNs) is largely mediated through cAMP signaling, as AC5 activity is promoted by the stimulation of the G protein-coupled dopamine receptors type 1 and adenosine receptors 2A [19].

Table 1 Synopsis of the most relevant genes associated with complex hyperkinetic movement disorders

Gene	Main associated phenotype	Gene product	Inheritance	Age of onset	Diagnostic clues
ADCY5	*ADCY5*-related chorea	Adenylate cyclase 5	AD/de novo	Infancy to childhood	Axial hypotonia and delayed milestones Diurnal and sleep-related MD exacerbations Dystonia and myoclonus prominent in some cases
PDE10A	*PDE10A*-related chorea	Phosphodiesterase 10A	De novo/AD/AR	Infancy to childhood	Delayed motor-language milestones and dysarthria in recessive cases MRI: symmetrical T2-hyperintense bilateral striatal lesions in cases with heterozygous de novo mutations
FOXG1	Congenital Rett disease	Forkhead Box G1	De novo	Infancy to early childhood	Severe ID, absent language, acquired microcephaly MRI: corpus callosum aplasia/hypoplasia, delayed myelination, simplified gyration
ARX	Early infantile epileptic encephalopathy-type 1; X-linked mental retardation	Aristaless-related homeobox protein	XL	Infancy	Ohtahara/West syndrome, severe mental retardation, generalized dystonia/dyskinesias with recurrent status dystonicus
STXBP1	Early infantile epileptic encephalopathy-type 4	Syntaxin-binding protein 1	De novo	Early infancy to childhood	Onset of seizures within one year of age. Developmental delay, ID, autistic-like features, ataxia with or without dyskinesias/dystonia
SYT1	Severe motor delay and intellectual disability	Synaptotagmin-1	De novo	Infancy	Severely delayed motor development without seizures
UNC13A	Congenital encephalopathy with dyskinesias	Unc-13 homolog A	De novo	Congenital	Developmental and speech delay; ID, congenital dyskinesias with intention tremor, rare febrile seizures
GNAO1	Early infantile epileptic encephalopathy type 17/Ohtahara syndrome	Gαo subunit of GPCR	De novo	Infancy to childhood	Developmental delay and ID Long-lasting MD exacerbations not related to sleep Epilepsy can be absent or well controlled
GRIN1	Mental retardation, autosomal dominant 8	GluN1 subunit of NMDAR	De novo/AR	Infancy	Severe developmental delay and ID Early-onset epileptic seizures Oculogyric crises Cortical blindness, dysmorphic traits, microcephaly
FRRS1L	Early infantile epileptic encephalopathy-type 37	Ferric Chelate Reductase 1-like	AR	Infancy	Psychomotor regression after normal development Severe encephalopathic epilepsy Choreo-athetosis in infancy/childhood, parkinsonism in adolescence
TBC1D24	Early infantile epileptic encephalopathy type 16	TBC1 domain family, member 24	AR	Infancy	Early-onset myoclonic seizures Variable degrees of ID Dystonia
GPR88	*GPR88*-related chorea	G protein-coupled receptor 88	AR	Infancy to childhood	Developmental and language delay Severe mental retardation Scarcely progressive chorea
KMT2B	DYT28 dystonia	lysine-specific histone methyltransferase 2B	De novo/AD	Childhood-adolescence	Onset in lower limbs and prominent oro-mandibular/laryngeal involvement Mild dysmorphic traits; mild ID Good and sustained response to pallidal DBS
ATP1A3	AHC RDP CAPOS syndrome	Na^+/K^+ ATPase, α3 subunit	De novo/AD	Infancy to fifth decade	Abrupt onset of neurological signs (dystonia, muscular weakness, ataxia) Initial hemisomatic distribution Identifiable triggering factors

MD, movement disorders; GPCR, guanine nucleotide-binding protein-coupled receptors; NMDAR, glutamatergic *N*-methyl-D-aspartate receptors; ID, intellectual disability; AHC, alternating hemiplegia of childhood; RDP, rapid-onset dystonia parkinsonism; CAPOS, cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss; DBS, deep brain stimulation

PDE10A-Related Disorders

Both dominant and recessive mutations in this gene have been recently reported in patients with childhood-onset chorea with a generalized distribution and also involving the facial muscles. Two recurrent dominant mutations (p.Phe300Leu and p.Phe334Leu) have been found so far in five unrelated patients worldwide, arising de novo in all but one subject, whose family showed a dominant pattern of inheritance with complete penetrance [20••, 21, 22]. Recessive homozygous mutations (p.Tyr107Cys and p.Ala116Pro) have been detected in eight patients from two consanguineous pedigrees [23••]. Clinically, carriers of dominant mutations display a homogeneous phenotype characterized by early onset (5–15 years) chorea, normal development and cognition, and characteristic symmetrical T2-hyperintense bilateral striatal lesions on brain MRI. Disease course seems to be non-progressive although diurnal fluctuations in childhood and a progressive spreading of chorea during life with increased severity in the elderly have been reported [20••, 21]. Also, levodopa-responsive parkinsonism with abnormal DAT-scan has been described in an adult positive patient [20••]. However, more evidence is needed to establish whether this is truly part of the *PDE10A*-realted phenotype in the elderly or a chance association. Patients carrying biallelic *PDE10A* mutations show a more severe phenotype, with markedly delayed motor and language milestones, axial hypotonia, an earlier age at onset of chorea (within 6 months of age), severe dysarthria, and mild ID in some cases. In a single affected subject, childhood-onset epilepsy was also reported. Despite a more severe neurological involvement, the MRI of these cases is normal, without striatal abnormalities observed in cases with dominant mutations [23••].

PDE10A encodes phosphodiesterase 10A, which regulates the degradation of cAMP and cGMP in MSNs of the corpus striatum, where it is highly and selectively expressed. Both recessive and dominant mutations in *PDE10A* have been shown to lead to a loss of enzymatic function or reduced striatal protein levels [20••, 23••].

Interestingly, preliminary evidence suggests that pathogenic mutations in *ADCY5* may act through a gain of function mechanism [4], overall supporting the hypothesis that abnormally increased levels of intracellular cAMP in striatal neurons may represent a key mechanism in the pathogenesis of chorea.

KMT2B-Related Disorders

KMT2B, also known as *MLL4*, encodes a ubiquitously expressed histone lysine methyltransferase involved in methylation of histone H3 at lysine 4 (H3K4). This gene, located on the chromosomal region 19q13.12, belongs to the SET/MLL family of proteins, which are essential for activating specific sets of genes during normal development [24]. Consistently, loss-of-function mutations in other MLL-encoding genes have been reported in a number of human developmental disorders, such as Kabuki syndrome [25]. Mutations in *KMT2B*, including interstitial microdeletions detected by microarray at 19q13.11-19q13.12, have been reported in patients with childhood-onset dystonia with a progressive course and a variable number of additional clinical features [26••, 27••]. Patients classically present with lower limb dystonia in early childhood, with subsequent generalization as observed in DYT1 mutation carriers; however, unlike DYT1 patients, affected subjects develop a prominent oromandibular and laryngeal involvement that can lead to severe dysarthria or even anarthria. Most cases carry de novo dominant mutations, but a limited number of families with an autosomal dominant transmission have been reported as well [27••, 28]. Intrafamilial clinical heterogeneity, with variable severity of dystonia as well as incomplete penetrance, either true o due to possible parental mosaicism have been observed [26••, 27]. So far, 33 unrelated patients carrying *KMT2B* variants with convincing evidence of pathogenicity have been reported, of which 19 carried genomic microdeletion involving *KMT2B* and different contiguous genes [16, 26••, 27••, 28]. *KMT2B*-related dystonia has been defined "complex" in that additional neurological and systemic features have been recognized in some of the mutation carriers, including psychomotor and language delay, minor dysmorphic traits and a characteristic facial appearance (bulbous nasal tips and elongated face), mild-to-moderate ID, short stature, skin abnormalities, and psychiatric disturbances [26••]. In some patients, the complexity of the clinical phenotype could be partially related to the extension of microdeletions on chromosome 19 leading to haploinsufficiency of a variable number of genes contiguous to *KMT2B*. Notably, a marked improvement of dystonia with sustained clinical benefit on long-term follow-up has been reported following bilateral GPi DBS, whereas no oral medication is reported to be particularly effective in alleviating motor manifestations [26••, 27••, 28].

Meyer et al. reported a detection rate of *KMT2B* mutations in up to 38% of patients with early-onset progressive dystonia, suggesting that the contribution of this recently discovered gene to the pathogenesis of childhood-onset dystonia is far higher than most other dystonia-related genes [26••].

ATP1A3-Related Disorders

ATP1A3 gene encodes the α3 isoform of the catalytic subunit of the Na^+/K^+ pump, which is an adenosine triphosphatase (ATPase) cation transporter playing a crucial role in maintaining electrochemical gradients for Na^+ and K^+ across the plasma membrane of different cellular types [29]. Mutations affecting the α3 subunit, which is selectively expressed in neurons, were initially linked to three distinct neurological

phenotypes, including rapid-onset dystonia parkinsonism (RDP), alternating hemiplegia of childhood (AHC), and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome [30–33]. Other presentations that do not fall within these neurological entities, as well as intermediate and overlapping phenotypes, have emerged in recent years, providing evidence that these conditions are different manifestations of a wide phenotypic spectrum rather than allelic disorders [34•, 35].

Mutations in *ATP1A3* arise de novo in most cases of AHC, whereas autosomal dominant transmission has been documented in RDP and CAPOS syndrome cases; moreover, germline mosaicism has been recently reported in two families with recurrence of AHC in offspring of unaffected parents [35, 36].

In AHC, symptoms begin before 18 months, and developmental delay is the rule. Clinical manifestations consist of paroxysmal episodes of unilateral hemiplegia or quadriplegia, dystonia, or oculomotor abnormalities (such as monocular nystagmus) which disappear upon sleeping, sometimes only transiently. Episodes last from minutes to several days and can occur with a variable frequency, up to multiple times a day. About half of cases develop epilepsy [37].

In RDP, patients present with abrupt onset of asymmetric dystonia with generally minor features of parkinsonism, with a clear rostro-caudal spreading (face > arm > leg) and prominent bulbar involvement. Symptoms evolve over a few minutes to 30 days, with subsequent stabilization within 1 month; disease course is often biphasic, with a sudden second worsening of symptoms during life. Age at onset ranges from infancy to the fifth decade [38].

In AHC and RDP, clinical manifestations are typically triggered by environmental, physical, or emotional stressors (excitement, strong emotions, physical exertion, febrile illness, excessive environmental stimuli—sounds, light, etc.). The recognition of provocative factors triggering paroxysmal neurological symptoms with an initial hemisomatic distribution represents the most pathognomonic feature to diagnose *ATP1A3*-related disorders and must be carefully investigated in the patients' clinical history [35].

Atypical phenotypes include paroxysms of unresponsiveness, bulbar signs, ataxia, fever-induced encephalopathy, prolonged flaccid tetraplegia with persistent choreo-athetosis between episodes, catastrophic epilepsy, and progressive childhood-onset cerebellar syndrome with step-wise deterioration [34•, 39–41].

From a genetic point of view, mutations are distributed over almost all *ATP1A3* coding sequence, but RPD phenotypes are mainly associated with mutations in exons 8, 14, and 17, whereas the majority of mutations in patients with AHC are located in exons 17 and 18 [34•]. Available evidence supports a genotype-phenotype correlation with mutations causing classic AHC affecting trans-membrane and functional protein domains; two recurrent missense mutations (p.Asp801Asn and p.Glu815Lys) have been detected in 50% of AHC cases reported. Moreover, only four missense variants have been detected so far in AHC-RDP intermediate phenotypes, and a single recurrent missense mutation (p.Glu818Lys) has been identified in all CAPOS cases [34•, 35].

No specific drugs targeting the altered ionic transport across the Na^+/K^+ pump are available, and symptomatic treatment of acute attacks mostly with benzodiazepines and other sleep inducers is the most frequent therapeutic approach in AHC. Flunarizine is widely used as a prophylactic agent; in a series of 30 AHC patients, it was effective to reduce frequency and duration of attacks in 50% of cases, but no controlled trials are available [42•]. Topiramate is also used with the same aim based on anecdotal reports. In RDP, treatment of dystonia and parkinsonism does not benefit from dopaminergic drugs, and GPi DBS has proven ineffective in a very limited number of cases and also in the authors' experience [43].

GPR88-Related Disorders

Alkufri et al. recently individuated a recessive homozygous truncating mutation (p.Cys291*) in *GPR88* in three affected children from a consanguineous Palestinian family [44•]. Patients (all females) presented with developmental delay in infancy, markedly delayed speech and learning disability followed, around 9 years of age, by chorea initially affecting the facial muscles and subsequently spreading to involve upper limbs (mainly distally), trunk, and tights. Chorea showed a slow but constant progression over a period of months, without further worsening few years after the onset. Severe mental retardation (IQ 40 in one subject) and a scarcely progressive movement disorder therefore seem to be key phenotypic features of this disorder. So far, no additional cases following the original publication have been reported.

The *GPR88* gene encodes a G protein-coupled receptor (GPCR) abundantly expressed both in D1R- and D2R-expressing MSNs, which are, respectively, part of the direct and indirect pathway [45].

MSNs from *GPR88* knock-out mice show increased glutamatergic excitability and reduced GABAergic inhibition, which results in enhanced firing rates in vivo, producing a murine phenotype characterized by hyperactivity, impaired motor coordination, and motor learning [46].

Hyperkinetic Movement Disorders in Epileptic-Dyskinetic Encephalopathies

Early onset encephalopathies are a heterogeneous group of diseases characterized by severe dysfunction of cognitive, sensory, and motor development. The etiology of these disorders is variable and includes acquired causes such as

prematurity, congenital infections and hypoxic insult at birth, as well as various genetic defects that disrupt brain function, or its normal structure and development. Early-onset, often drug-resistant seizures are a recurrent feature of several encephalopathies. In recent years, the co-occurrence of hyperkinetic movement disorders (chorea, dystonia, ballismus, complex stereotypies) in early-onset epileptic encephalopathies (EOEE) has been increasingly recognized and detailed, to the point that movement disorders are now considered a core feature of several EOEE. These conditions, currently referred to as "epileptic-dyskinetic encephalopathies" (MIM: 308350), are clinically and genetically heterogeneous and encompass various degrees of ID and severe, often intractable epilepsy in association with hyperkinetic movement disorders. Altered functioning of glutamatergic NMDA and AMPA receptors as well as impaired neurotransmission and synaptic plasticity in early neurodevelopmental stages seem to be relevant pathogenetic mechanisms that can give rise to a wide spectrum of variably associated neurological symptoms including movement disorders, ID, and epilepsy.

FOXG1-Related Disorders

FOXG1 (Forkhead Box G1) gene, a transcription repressor, plays a crucial role in fetal telencephalon development and is an important component of the transcription regulatory network that controls proliferation, differentiation, neurogenesis, and neurite outgrowth in the cerebral cortex, hippocampus, and basal ganglia [47, 48]. Mutations in *FOXG1* cause a distinct developmental encephalopathy manifesting in infancy or early childhood with severe developmental delay, acquired microcephaly, profound ID, epilepsy, and absent language (so called "congenital Rett syndrome"; OMIM 613454) [49]. Corpus callosum hypoplasia or aplasia, delayed myelination, simplified gyration, and fronto-temporal abnormalities are frequent radiological findings. Beyond these core features, the phenotypic spectrum of *FOXG1* mutations has recently expanded to include early-onset, complex hyperkinetic movement disorders featuring various combinations of chorea, dystonia, dyskinesia, myoclonus, and hand stereotypies that are virtually observed in all positive patients and become evident since the first years of life [50]. In a series of 28 patients, chorea was the most frequent movement disorder (88%), followed by orolingual/facial dyskinesia (80%) and dystonia (76%); movement disorder course was progressive in about half of cases, with remarkable severity and disability [51••]. In a recent review of 83 novel and published cases, dyskinesias and hand stereotypies were both reported in 90% of patients whose clinical data were available. A definite genotype-phenotype correlation has not been established, although truncating *FOXG1* mutations in the N-terminal and the forkhead domains (except conserved site 1) are associated with more severe phenotypes, whereas missense variants in the forkhead conserved site 1 seem to be responsible for milder phenotypes, with independent ambulation, spoken language, normal head growth, and ability to use hands [51••, 52].

Several drugs have shown little or no benefit in alleviating *FOXG1* movement disorders, although levodopa, tetrabenazine, and pimozide were partially beneficial in single cases [50, 51••].

Hyperkinetic movements similar to those observed in *FOXG1* have also been reported in carriers of *CDKL5* mutations, transmitted as an X-linked trait. Mutations in this gene are associated with variant Rett syndrome characterized by onset of refractory seizures within the first weeks of life inconstantly associated with movement disorders [53].

The differential diagnosis of *FOXG1*-related phenotypes includes other epileptic-dyskinetic encephalopathies such as *ARX*-related encephalopathy (characterized by infantile spasms, neonatal-onset progressive dystonia with recurrent status dystonicus, and severe mental retardation) and three conditions caused by de novo mutations in genes essential for neurotransmitter release through synaptic vesicle fusion [54–56]. These include mutations in *STXBP1* (featuring infantile-onset epilepsy with good prognosis, tremor, and frequent paroxysmal non-epileptic movement disorders), *SYT1* (associated with severe developmental delay and an early onset, paroxysmal dyskinetic movement disorder worsening at night), and *UNC13A* (linked to developmental and speech delay, ID, dyskinesias, and intention tremor, with febrile seizures as a minor feature) [57–59].

GNAO1-Related Disorders

GNAO1 encodes a subclass (Gαo) of the Gα subunit of heterotrimeric guanine nucleotide-binding proteins which is highly expressed in the brain, where it is involved in the regulation of neuronal excitability and neurotransmission. De novo mutations in *GNAO1* were initially associated with Ohtahara syndrome, a severe type of early epileptic encephalopathy characterized by neonatal tonic spasms, severe motor developmental delay, and ID with a suppression-burst pattern on EEG [60, 61]. *GNAO1*-related encephalopathy has been further characterized following the individuation of additional mutation carriers, and hyperkinetic movements have emerged as an important core feature, being universally present in affected subjects. Patients present in most cases a combination of generalized chorea associated with dystonia, which manifest within the first months or years of life, with a median age at onset around 2 years [62••]. Facial and oro-lingual dyskinesia and complex stereotypies have been reported as well. Movement disorders display a chronic course with characteristic episodic exacerbations triggered by high temperature, infections, emotions, and purposeful movements lasting from minutes to days and even months and often being accompanied by dysautonomic manifestations (sweating, tachycardia,

hypertemia, diaphoresis) and thus being potentially life-threatening [63]. Exacerbations have a variable frequency and can present in clusters up to several times a day. While developmental delay and severe ID are features consistently associated with *GNAO1* mutations, epilepsy is variably present and often follows the onset of movement disorders of months or years [64•].

So far, 45 genetically proven patients have been reported, harboring 25 different mutations (23 missense, one splice site, one deletion) [62••, 64•, 65–69]. Glutamine at position 246 (Glu246) and arginine at position 209 (Arg209), both highly conserved amino acids, are *GNAO1* mutational hotspots, and missense mutations involving these residues have been reported in about half (21/45, 46.7%) of published cases. A genotype-phenotype correlation has recently been suggested in functional in vitro studies, with *GNAO1* loss-of-function mutations associated with epileptic encephalopathy and gain-of-function or normally functioning alleles leading to phenotypes dominated by movement disorders [70••].

Tetrabenazine and neuroleptics seem to be the most effective drugs to treat movement disorders in *GNAO1* mutation carriers; in severe drug-resistant cases, bilateral GPi DBS has significantly improved the frequency and severity of exacerbations as well as patients' motor performances, although the baseline movement disorder seems to remain rather constant even after DBS implant [66, 71,72].

GRIN1-Related Disorders

GRIN1 encodes the GluN1 subunit of the glutamatergic *N*-methyl-D aspartate receptors (NMDAR), which are heteromeric protein complexes acting as ion channels upon ligand activation [73]. GluN1 subunits have a key role in the plasticity of synapses, which underlies memory and learning [74]. De novo heterozygous variants of *GRIN1* were first linked to non-syndromic ID with or without epilepsy [75]. So far, 34 positive patients from 30 different families have been reported [76, 77•, 78–80]. The vast majority of mutations are heterozygous variants arising de novo, but recessive biallelic mutations have also been described in seven patients from three different consanguineous kindred [77•, 78]. *GRIN1* positive patients present in almost all cases with severe developmental delay, cognitive dysfunction, and profound ID since early infancy. About 70% of cases develop early-onset, polymorphic seizures with non-specific EEG patterns that are drug-resistant in about one third of cases. Hyperkinetic movement disorders (mainly a combination of chorea and dystonia) have been observed in about 60% of patients, and complex stereotypies as well as oculogyric crises resembling those of monoamine neurotransmitter disorders are frequently reported, being an important diagnostic clue [77•]. Additional features include spastic tetraparesis, cortical blindness, non-specific sleep disturbances, subtle dysmorphism, and microcephaly. All de novo *GRIN1* mutations cluster within or in close proximity of the transmembrane domains of GluN1, a highly-conserved region; in vitro studies demonstrated that variants in this position lead to a dominant negative effect, whereas one of the reported homozygous variants (c.649C>T; p.Arg217Trp) causes impaired activation of the NMDA receptor [77•]. Moreover, a *GRIN1* truncating variant (c.1666C>T; p.Gln556*), resulting in GRIN1 haploinsufficiency, seems to be tolerated in a heterozygous state, not producing a neurological phenotype; however, when in homozygosity, it has proven responsible for a fatal neonatal epileptic encephalopathy [77•].

FRRS1L-Related Disorders

The *FRRS1L* gene encodes a component of the outer core of AMPA receptor accessory proteins. Glutamatergic AMPA receptors represent the most common receptor subtype in the brain, mediating fast glutamatergic excitatory postsynaptic potentials. Using a combination of homozygosity mapping and WES, Madeo et al. recently identified four different homozygous mutations in *FRRS1L* in eight patients from four different pedigrees, two of which were consanguineous [81••]. Six additional patients from a large consanguineous Arab kindred have subsequently been reported [82]. Affected subjects present around 20 months of age with psychomotor regression after a phase of normal development, followed by the onset of progressive choreoathetosis and ballismus and severe encephalopathic epilepsy. Differently from *GNAO1* positive patients, the severity of movement disorders seems to decrease over disease course, giving way to an akinetic-rigid phenotype in late adolescence, and no episodic exacerbations have been reported [81••].

TBC1D24-Related Disorders

TBC1D24 is involved in synaptic vesicles trafficking and is expressed in multiple human tissues, with the highest expression in the brain [83]. Recessive homozygous or compound heterozygous mutations in *TBC1D24* have been linked to several human diseases, ranging from non-syndromic deafness to a wide spectrum of epilepsies, whereas dominant mutations have been linked to a type of non-syndromic hearing loss. The most common epilepsy phenotype consists of early-onset myoclonic epilepsy, myoclonic seizures (often occurring in clusters), and drug-resistance. About 50 epileptic patients carrying *TBC1D24* have been reported worldwide, with heterogeneous presentations and prognosis [84•]. In a recent review of new and published cases, 39/48 (81%) presented mild to profound intellectual

disability, which therefore appears to be a frequently encountered clinical feature. Moreover, dystonia (sometimes with a hemisomatic distribution) was reported in 7/48 (14.5%) of patients as well as in a recently published case with a complex phenotype including epilepsy, infantile-onset parkinsonism, cerebellar signs, and psychosis [85]. Cortical myoclonus affecting lower limbs with gait impairment has also been reported [86].

Conclusions

In the last 5 years, the list of genes associated with dystonia, chorea, myoclonus, and mixed movement disorders has dramatically expanded and so has the phenotype associated with mutations in individual genes.

Our systematic review of the recent literature shows that an unexpected variety of molecular causes underlie complex hyperkinetic disorders. Several genes, though individually very are, can be responsible for the same phenotypes and, on the other hand, mutations in a given gene can be associated with several phenotypes, which are often part of spectrum and not discrete entities (as exemplified by *ATP1A3*-related disorders). With some exceptions (e.g., *ADCY5*-, *KMT2B*-, *ATP1A3*-related movement disorders), the number of reported patients affected by these novel genetic entities is still rather limited. Therefore, our knowledge about the clinical features and natural history of these disorders will only grow once larger case series will become available.

Importantly, NGS is challenging the traditional—and often problematic—approach to patients with hyperkinetic movement disorders, based on the recognition of "core clinical features." The increasing availability of NGS in clinical practice will hopefully help to formulate definite diagnoses in a larger number of patients affected by complex movement disorders, allowing clinicians to provide families with appropriate genetic counseling and disease-specific therapies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Abdo WF, van de Warrenburg BP, Burn DJ, Quinn NP, Bloem BR. The clinical approach to movement disorders. Nat Rev Neurol. 2010;6:29–37.
2.• Chen YZ, Matsushita MM, Robertson P, Rieder M, Girirajan S, Antonacci F, et al. Autosomal dominant familial dyskinesia and facial myokymia: single exome sequencing identifies a mutation in adenylyl cyclase 5. Arch Neurol. 2012;69:630–5. **This paper identifies for the first time a pathogenic mutation in *ADCY5* as the cause of familial dyskinesia and facial myokymia, an autosomal dominant movement disorder previously described by Fernandez et al. in a large dominant kindred.**
3. Fernandez M, Raskind W, Wolff J, Matsushita M, Yuen E, Graf W, et al. Familial dyskinesia and facial myokymia (FDFM): a novel movement disorder. Ann Neurol. 2001;49:486–92.
4. Chen YZ, Friedman JR, Chen DH, Chan GC, Bloss CS, Hisama FM, et al. Gain-of-function ADCY5 mutations in familial dyskinesia with facial myokymia. Ann Neurol. 2014;75:542–9.
5.• Mencacci NE, Erro R, Wiethoff S, Hersheson J, Ryten M, Balint B, et al. ADCY5 mutations are another cause of benign hereditary chorea. Neurology. 2015;85:80–8. **By studying 18 unrelated cases diagnosed with benign hereditary chorea without *NKX2-1* mutations, the authors identify the *ADCY5* p.R418W mutation in two cases showing chorea with a progressive course, in contrast to BHC secondary to *NKX2-1* mutations. This difference in the clinical course is mirrored by brain expression data, showing increasing *ADCY5* expression in the striatum during brain development, whereas *NKX2-1* shows an opposite trend.**
6.•• Chen DH, Méneret A, Friedman JR, Korvatska O, Gad A, Bonkowski ES, et al. ADCY5-related dyskinesia: broader spectrum and genotype-phenotype correlations. Neurology. 2015;85:2026–35. **This paper reports the identification of 3 new families and 12 new sporadic cases carrying *ADCY5* mutations. The authors provide a detailed description of *ADCY5*-related phenotype to include a mixed hyperkinetic disorder characterized by chorea, dystonia and myoclonus preceded by axial hypotonia and developmental delay in infancy/childhood.**
7. Carapito R, Paul N, Untrau M, Le Gentil M, Ott L, Alsaleh G, et al. A de novo ADCY5 mutation causes early-onset autosomal dominant chorea and dystonia. Mov Disord. 2015;30:423–7.
8. Chang FC, Westenberger A, Dale RC, Smith M, Pall HS, Perez-Dueñas B, et al. Phenotypic insights into ADCY5-associated disease. Mov Disord. 2016;31:1033–40.
9. Dy ME, Chang FC, Jesus SD, Anselm I, Mahant N, Zeilman P, et al. Treatment of ADCY5-associated dystonia, chorea, and hyperkinetic disorders with deep brain stimulation: a multicenter case series. J Child Neurol. 2016;31:1027–35.
10. Zech M, Boesch S, Jochim A, Weber S, Meindl T, Schormair B, et al. Clinical exome sequencing in early-onset generalized dystonia and large-scale resequencing follow-up. Mov Disord. 2017;32:549–59.
11. Meijer IA, Miravite J, Kopell BH, Lubarr L. Deep brain stimulation in an additional patient with ADCY5-related movement disorder. J Child Neurol. 2017;32:438–9.
12. Westenberger A, Max C, Brüggemann N, Domingo A, Grütz G, Pawlack H, et al. Alternating hemiplegia of childhood as a new presentation of adenylate cyclase 5-mutation-associated disease: a report of two cases. J Pediatr. 2017;181:306–8.

13. Douglas AG, Andreoletti G, Talbot K, Hammans SR, Singh J, Whitney A, et al. ADCY5-related dyskinesia presenting as familial myoclonus-dystonia. Neurogenetics. 2017;18:111–7.
14. Tunc S, Brüggemann N, Baaske MK, Hartmann C, Grütz K, Westenberger A, et al. Facial twitches in ADCY5-associated disease—myokymia or myoclonus? An electromyography study. Parkinsonism Relat Disord. 2017;40:73–5.
15.• Carecchio M, Mencacci NE, Iodice A, Pons R, Panteghini C, Zorzi G, et al. ADCY5-related movement disorders: frequency, disease course and phenotypic variability in a cohort of paediatric patients. Parkinsonism Relat Disord. 2017;41:37–43. **In this paper, the authors describe clinical features and disease course of six additional *ADCY5* mutation carriers, highlighting that paroxysms of chorea and/or dystonia can precede the onset of a chronic movement disorder and that the clinical picture can vary over time, sometimes leading to a spontaneous improvement of episodic exacerbations triggered by sleep or other provoking factors.**
16. Zech M, Jech R, Wagner M, Mantel T, Boesch S, Nocker M, et al. Molecular diversity of combined and complex dystonia: insights from diagnostic exome sequencing. Neurogenetics. 2017, ***in press***; https://doi.org/10.1007/s10048-017-0521-9.
17. Kinugawa K, Vidailhet M, Clot F, Apartis E, Grabli D, Roze E. Myoclonus-dystonia: an update. Mov Disord. 2009;24:479–89.
18. Friedman JR, Méneret A, Chen DH, Trouillard O, Vidailhet M, Raskind WH, et al. ADCY5 mutation carriers display pleiotropic paroxysmal day and nighttime dyskinesias. Mov Disord. 2016;31:147–8.
19. Hervé D. Identification of a specific assembly of the g protein golf as a critical and regulated module of dopamine and adenosine-activated cAMP pathways in the striatum. Front Neuroanat. 2011;5:48.
20.•• Mencacci NE, Kamsteeg E-J, Nakashima K, R'Bibo L, Lynch DS, Balint B, et al. De novo mutations in PDE10A cause childhood-onset chorea with bilateral striatal lesions. American J Hum Gen. 2016;98:763–71. ***PDE10A de novo* mutations are reported for the first time in patients with childhood-onset chorea and characteristic bilateral striatal lesions on brain MRI, confirming the crucial role of cAMP signalling in the regulation of striatal medium spiny neurons firing and the pathogenesis of chorea.**
21. Esposito S, Carecchio M, Tonduti D, Saletti V, Panteghini C, Chiapparini L, et al. A PDE10A de novo mutation causes childhood-onset chorea with diurnal fluctuations. Mov Disord. 2017; ***in press***
22. Myatake S, Koshimizu E, Shirai I, Kumada S, Nakata I, Kamemaru A, et al. A familial case of PDE10A-associated childhood-onset chorea with bilateral striatal lesions. Mov Disord. 2017; ***in press***
23.•• Diggle CP, Sukoff Rizzo SJ, Popiolek M, Hinttala R, Schülke JP, Kurian MA, et al. Biallelic mutations in PDE10A lead to loss of striatal PDE10A and a hyperkinetic movement disorder with onset in infancy. Am J Hum Gen. 2016;98:735–43. **Back-to-back publication with ref. 19, this paper describes the identification of recessive *PDE10A* mutations in patients with a more complex phenotype including chorea with onset in infancy, axial hypotonia and developmental delay. Patients' brain MRI was unremarkable, with no striatal lesions as described by Mencacci *et al*. in dominant mutations carriers, suggesting different *in vivo* mechanisms of the mutations.**
24. Shao GB, Chen JC, Zhang LP, Huang P, HY L, Jin J, et al. Dynamic patterns of histone H3 lysine 4 methyltransferases and demethylases during mouse preimplantation development. In Vitro Cell Dev Biol Anim. 2014;50:603–13.
25. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet. 2010;42:790–3.
26.•• Meyer E, Carss KJ, Rankin J, Nichols JM, Grozeva D, Joseph AP, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet. 2017;49:223–37. **In this multicentric international study, the authors identify 27 unrelated cases carrying dominant, mostly *de novo* mutations in *KMT2B*, a novel disease-causing gene located on chromosome 19. The patients' phenotype is characterized by childhood-onset generalized dystonia with onset in the lower limbs and prominent oromandibular and laryngeal involvement. Additional neurological and non-neurological features are reported, including developmental delay, minor facial dysmorphisms, and mild mental retardation.**
27.•• Zech M, Boesch S, Maier EM, Borggraefe I, Vill K, Laccone F, et al. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. Am J Hum Genet. 2016;99:1377–87. **Published in parallel with the manuscript by Meyer *et al*., this study reports different *KMT2B* mutation carriers with strikingly similar clinical features. The authors demonstrate significantly decreased mRNA levels of KMT2B in mutant fibroblasts, thus suggesting haploinsufficiency as the underlying pathogenic mechanism leading to dystonia.**
28. Zech M, Jech R, Havránková P, Fečíková A, Berutti R, Urgošík D, et al. KMT2B rare missense variants in generalized dystonia. Mov Disord. 2017; ***in press***
29. Shull GE, Greeb J, Lingrel JB. Molecular cloning of three distinct forms of the Na^+, K^+-ATPase α-subunit from rat brain. Biochemistry. 1986;25:8125–32.
30. de Carvalho Aguiar P, Sweadner KJ, Penniston JT, Zaremba J, Liu L, Caton M, et al. Mutations in the Na+/K+-ATPase alpha3 gene ATP1A3 are associated with rapid-onset dystonia parkinsonism. Neuron. 2004;43:169–75.
31. Heinzen EL, Swoboda KJ, Hitomi Y, Gurrieri F, Nicole S, de Vries B, et al. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. Nat Genet. 2012;44:1030–4.
32. Rosewich H, Thiele H, Ohlenbusch A, Maschke U, Altmüller J, Frommolt P, et al. Heterozygous de-novo mutations in ATP1A3 in patients with alternating hemiplegia of childhood: a whole-exome sequencing gene-identification study. Lancet Neurol. 2012;11:764–73.
33. Demos MK, van Karnebeek CD, Ross CJ, Adam S, Shen Y, Zhan SH, et al. A novel recurrent mutation in ATP1A3 causes CAPOS syndrome. Orphanet J Rare Dis. 2014;9:15.
34.• Rosewich H, Ohlenbusch A, Huppke P, Schlotawa L, Baethmann M, Carrilho I, et al. The expanding clinical and genetic spectrum of ATP1A3-related disorders. Neurology. 2014;82:945–55. **This paper provides important insights in the clinical spectrum of *ATP1A3*-associated disorders, highlighting the existence of partially overlapping phenotypes and making important observations on genotype-phenotype correlation, localization and clustering of *ATP1A3* mutations in 19 novel and 164 published cases.**
35. Sweney MT, Newcomb TM, Swoboda KJ. The expanding spectrum of neurological phenotypes in children with ATP1A3 mutations, alternating hemiplegia of childhood, rapid-onset dystonia-parkinsonism, CAPOS and beyond. Pediatr Neurol. 2015;52:56–64.
36. Hully M, Ropars J, Hubert L, Boddaert N, Rio M, Bernardelli M, et al. Mosaicism in ATP1A3-related disorders: not just a theoretical risk. Neurogenetics. 2017;18:23–8.
37. Rosewich H, Sweney MT, DeBrosse S, Ess K, Ozelius L, Andermann E, et al. Research conference summary from the 2014 International Task Force on ATP1A3-Related Disorders. Neurol Genet. 2017;e139:3.
38. Brashear A, Dobyns WB, de Carvalho Aguiar P, et al. The phenotypic spectrum of rapid-onset dystonia-parkinsonism (RDP) and mutations in the ATP1A3 gene. Brain. 2007;130:828–35.

39. Yano ST, Silver K, Young R, DeBrosse SD, Ebel RS, Swoboda KJ, et al. Fever-induced paroxysmal weakness and encephalopathy, a new phenotype of ATP1A3 mutation. Pediatr Neurol. 2017;73: 101–5.
40. Kanemasa H, Fukai R, Sakai Y, Torio M, Miyake N, Lee S, et al. De novo p.Arg756Cys mutation of ATP1A3 causes an atypical form of alternating hemiplegia of childhood with prolonged paralysis and choreoathetosis. BMC Neurol. 2016;16:174.
41. Jaffer F, Fawcett K, Sims D, Heger A, Houlden H, Hanna MG, et al. Familial childhood-onset progressive cerebellar syndrome associated with the ATP1A3 mutation. Neurol Genet. 2017;e145:3.
42.• Pisciotta L, Gherzi M, Stagnaro M, Calevo MG, Giannotta M, Vavassori MR, et al. Alternating hemiplegia of childhood: pharmacological treatment of 30 Italian patients. Brain Dev. 2017;39:521–8. **This is the first paper systematically assessing the available evidence about the efficacy and outcome of different treatments used in Alternating Hemiplegia of Childhood due to *ATP1A3* mutations and is relevant for clinicians dealing with this rare disorder.**
43. Deutschlander A, Asmus F, Gasser T, Steude U, Botzel K. Sporadic rapid-onset dystonia-parkinsonism syndrome: failure of bilateral pallidal stimulation. Mov Disord. 2005;20:254–7.
44.• Alkufri F, Shaag A, Abu-Libdeh B, Elpeleg O. Deleterious mutation in GPR88 is associated with chorea, speech delay, and learning disabilities. Neurol Genet. 2016;2:e64. **A combination of marked developmental and speech delay, intellectual disability and chorea is described in association with a homozygous mutation in *GPR88*, an orphan G protein-coupled receptor selectively expressed in striatal medium spiny neurons.**
45. Massart R, Guilloux JP, Mignon V, Sokoloff P, Diaz J. Striatal GPR88 expression is confined to the whole projection neuron population and is regulated by dopaminergic and glutamatergic afferents. Eur J Neurosci. 2009;30:397–414.
46. Quintana A, Sanz E, Wang W, Storey GP, Güler AD, Wanat MJ, et al. Lack of GPR88 enhances medium spiny neuron activity and alters motor- and cue-dependent behaviors. Nature Neurosci. 2012;15:1547–55.
47. Regad T, Roth M, Bredenkamp N, Illing N, Papalopulu N. The neural progenitor-specifying activity of FoxG1 is antagonistically regulated by CKI and FGF. Nat Cell Biol. 2007;9:531–40.
48. Brancaccio M, Pivetta C, Granzotto M, Filippis C, Mallamaci A. Emx2 and Foxg1 inhibit gliogenesis and promote neuronogenesis. Stem Cells. 2010;28:1206–18.
49. Ariani F, Hayek G, Rondinella D, Artuso R, Mencarelli MA, Spanhol-Rosseto A, et al. FOXG1 is responsible for the congenital variant of Rett syndrome. Am J Hum Genet. 2008;83:89–93.
50. Cellini E, Vignoli A, Pisano T, Falchi M, Molinaro A, Accorsi P, et al. The hyperkinetic movement disorder of FOXG1-related epileptic-dyskinetic encephalopathy. Dev Med Child Neurol. 2016;58: 93–7.
51.•• Papandreou A, Schneider RB, Augustine EF, Ng J, Mankad K, Meyer E, et al. Delineation of the movement disorders associated with FOXG1 mutations. Neurology. 2016;86:1794–800. **In this series of 28 patients, the authors highlight for the first time that hyperkinetic movement disorders are a cardinal feature of *FOXG1*-related phenotypes and consist mostly of a combination of chorea, dystonia and myoclonus.**
52. Mitter D, Pringsheim M, Kaulisch M, Plümacher KS, Schröder S, Warthemann R, et al. FOXG1 syndrome: genotype-phenotype association in 83 patients with FOXG1 variants. Genet Med. 2017; ***in press***
53. Kobayashi Y, Tohyama J, Kato M, Akasaka N, Magara S, Kawashima H, et al. High prevalence of genetic alterations in early-onset epileptic encephalopathies associated with infantile movement disorders. Brain and Development. 2016;38:285–92.
54. Guerrini R, Moro F, Kato M, Barkovich AJ, Shiihara T, McShane MA, et al. Expansion of the first polyA tract of ARX causes infantile spasms and status dystonicus. Neurology. 2007;69:427–33.
55. Poirier K, Eisermann M, Caubel I, Kaminska A, Peudonnier S, Boddaert N, et al. Combination of infantile spasms, non-epileptic seizures and complex movement disorder: a new case of ARX-related epilepsy. Epilepsy Res. 2008;80:224–8.
56. Absoud M, Parr JR, Halliday D, Pretorius P, Zaiwalla Z, Jayawant SA. Novel ARX phenotype: rapid neurodegeneration with Ohtahara syndrome and a dyskinetic movement disorder. Dev Med Child Neurol. 2010;52:305–7.
57. Deprez L, Weckhuysen S, Holmgren P, Suls A, Van Dyck T, Goossens D, et al. Clinical spectrum of early-onset epileptic encephalopathies associated with STXBP1 mutations. Neurology. 2010;75:1159–65.
58. Baker K, Gordon SL, Grozeva D, van Kogelenberg M, Roberts NY, Pike M, et al. Identification of a human synaptotagmin-1 mutation that perturbs synaptic vesicle cycling. J Clin Invest. 2015;125: 1670–8.
59. Lipstein N, Verhoeven-Duif NM, Michelassi FE, Calloway N, van Hasselt PM, Pienkowska K, et al. Synaptic UNC13A protein variant causes increased neurotransmission and dyskinetic movement disorder. J Clin Invest. 2017;127:1005–18.
60. Nakamura K, Kodera H, Akita T, Shiina M, Kato M, Hoshino H, et al. De novo mutations in GNAO1, encoding a $G_{\alpha o}$ subunit of heterotrimeric G proteins, cause epileptic encephalopathy. Am J Hum Genet. 2013;93:496–505.
61. Ohtahara S, Yamatogi Y. Ohtahara syndrome: with special reference to its developmental aspects for differentiating from early myoclonic encephalopathy. Epilepsy Res. 2006;70:S58–67.
62.•• Danti FR, Galosi S, Romani M, Montomoli M, Carss KJ, Raymond FL, et al. GNAO1 encephalopathy: broadening the phenotype and evaluating treatment and outcome. Neurol Genet. 2017;3:e143. **The authors of this paper report the clinical and genetic features of 7 novel and 20 previously reported *GNAO1* mutation carriers underlying that episodic, often long-lasting exacerbations of movement disorders are an important diagnostic clue, and individuating two mutational hot spots of GNAO1 (Arg209 and Glu246).**
63. Ananth AL, Robichaux-Viehoever A, Kim YM, Hanson-Kahn A, Cox R, Enns GM, et al. Clinical course of six children with GNAO1 mutations causing a severe and distinctive movement disorder. Pediatr Neurol. 2016;59:81–4.
64.• Saitsu H, Fukai R, Ben-Zeev B, Sakai Y, Mimaki M, Okamoto N, et al. Phenotypic spectrum of GNAO1 variants: epileptic encephalopathy to involuntary movements with severe developmental delay. Eur J Hum Genet. 2016;24:129–34. **A paper providing a characterization of the heterogeneous and complex clinical expression of *GNAO1* mutations, blurring the boundaries between epilepsy and hyperkinetic movement disorders.**
65. Bruun TUJ, DesRoches CL, Wilson D, Chau V, Nakagawa T, Yamasaki M, et al. Prospective cohort study for identification of underlying genetic causes in neonatal encephalopathy using whole-exome sequencing. Genet Med. 2017; ***in press***
66. Waak M, Mohammad SS, Coman D, Sinclair K, Copeland L, Silburn P, et al. GNAO1-related movement disorder with life-threatening exacerbations: movement phenomenology and response to DBS. J Neurol Neurosurg Psychiatry. 2017; ***in press***
67. Schorling DC, Dietel T, Evers C, Hinderhofer K, Korinthenberg R, Ezzo D, et al. Expanding phenotype of de novo mutations in GNAO1: four new cases and review of literature. Neuropediatrics. 2017; ***in press***
68. Arya R, Spaeth C, Gilbert DL, Leach JL, Holland KD. GNAO1-associated epileptic encephalopathy and movement disorders: c.607G>A variant represents a probable mutation hotspot with a distinct phenotype. Epileptic Disord. 2017;19:67–75.

69. Sakamoto S, Monden Y, Fukai R, Miyake N, Saito H, Miyauchi A, et al. A case of severe movement disorder with GNAO1 mutation responsive to topiramate. Brain and Development. 2017;39:439–43.

70.•• Feng H, Sjögren B, Karaj B, Shaw V, Gezer A, Neubig RR. Movement disorder in GNAO1 encephalopathy associated with gain-of-function mutations. Neurology. 2017;89:762–70. **A paper providing for the first time evidence of the molecular mechanisms underlying the wide spectrum of clinical manifestations of *GNAO1* mutations. By studying in vitro the impact of human mutant alleles on $G_{\alpha 0}$ synthesis, Feng and colleagues suggest that loss-of-function *GNAO1* mutations are associated with epileptic encephalopathy (Ohtahara syndrome), whereas gain-of-function or normally-functioning mutants are responsible for hyperkinetic movement disorder without epilepsy.**

71. Kulkarni N, Tang S, Bhardwaj R, Bernes S, Grebe TA. Progressive movement disorder in brothers carrying a GNAO1 mutation responsive to deep brain stimulation. J Child Neurol. 2016;31:211–4.

72. Yilmaz S, Turhan T, Ceylaner S, Gökben S, Tekgul H, Serdaroglu G. Excellent response to deep brain stimulation in a young girl with GNAO1-related progressive choreoathetosis. Childs Nerv Syst. 2016;32:1567–8.

73. Traynelis SF, Wollmuth LP, McBain CJ, Menniti FS, Vance KM, Ogden KK, et al. Glutamate receptor ion channels: structure, regulation, and function. Pharmacol Rev. 2010;62:405–96.

74. Lau CG, Zukin RSNMDA. Receptor trafficking in synaptic plasticity and neuropsychiatric disorders. Nat Rev Neurosci. 2007;8:413–26.

75. Hamdan FF, Gauthier J, Araki Y, Lin DT, Yoshizawa Y, Higashi K, et al. Excess of de novo deleterious mutations in genes associated with glutamatergic systems in nonsyndromic intellectual disability. Am J Hum Genet. 2011;88:306–16.

76. Ohba C, Shiina M, Tohyama J, Haginoya K, Lerman-Sagie T, Okamoto N, et al. GRIN1 mutations cause encephalopathy with infantile-onset epilepsy, and hyperkinetic and stereotyped movement disorders. Epilepsia. 2015;56:841–8.

77.• Lemke JR, Geider K, Helbig KL, Heyne HO, Schütz H, Hentschel J, et al. Delineating the GRIN1 phenotypic spectrum: a distinct genetic NMDA receptor encephalopathy. Neurology. 2016;86:2171–8. **A paper delineating the phenotypic spectrum of *de novo* and biallelic mutations in *GRIN1* in 23 patients (both novel and previously reported). The authors indicate profound intellectual disability, a mixed dystonic-dyskinetic movement disorder and oculogyric crises as characteristic phenotypic features. They also characterize functional consequences of *GRIN1* mutations demonstrating that an altered activity of the GluN1 subunit, encoded by *GRIN1*, leads to a loss of normal NMDA receptor function and represents the underlying pathogenic molecular mechanism in affected patients.**

78. Rossi M, Chatron N, Labalme A, Ville D, Carneiro M, Edery P, et al. Novel homozygous missense variant of GRIN1 in two sibs with intellectual disability and autistic features without epilepsy. Eur J Hum Genet. 2017;25:376–80.

79. Chen W, Shieh C, Swanger SA, Tankovic A, Au M, McGuire M, et al. GRIN1 mutation associated with intellectual disability alters NMDA receptor trafficking and function. J Hum Genet. 2017;62:589–97.

80. Zehavi Y, Mandel H, Zehavi A, Rashid MA, Straussberg R, Jabur B, et al. De novo GRIN1 mutations: an emerging cause of severe early infantile encephalopathy. Eur J Med Genet. 2017;60:317–20.

81.•• Madeo M, Stewart M, Sun Y, Sahir N, Wiethoff S, Chandrasekar I, et al. Loss-of-function mutations in FRRS1L lead to an epileptic-dyskinetic encephalopathy. Am J Hum Genet. 2016;98:1249–55. **The authors individuate biallelic mutations in *FRRS1L* as the cause of an epileptic-dyskinetic encephalopathy characterized by initially normal psychomotor development followed by a phase of regression, intractable epilepsy and prominent choreo-athetosis. Chronic alteration of GABAergic neurotransmission in the brain is proposed as the pathogenetic mechanism giving rise to this complex clinical entity.**

82. Shaheen R, Al Tala S, Ewida N, Abouelhoda M, Alkuraya FS. Epileptic encephalopathy with continuous spike-and-wave during sleep maps to a homozygous truncating mutation in AMPA receptor component FRRS1L. Clin Genet. 2016;90:282–3.

83. Campeau PM, Kasperaviciute D, JT L, Burrage LC, Kim C, Hori M, et al. The genetic basis of DOORS syndrome: an exome-sequencing study. Lancet Neurol. 2014;13:44–58.

84.• Balestrini S, Milh M, Castiglioni C, Lüthy K, Finelli MJ, Verstreken P, et al. TBC1D24 genotype-phenotype correlation: Epilepsies and other neurologic features. Neurology. 2016;87:77–85. **This paper provides a comprehensive review of 48 patients carrying mutations in *TBC1D24*. Detailed EEG findings, neuroimaging, developmental and cognitive features, treatment responsiveness are analysed, delineating the clinical phenotype associated with mutations in this gene.**

85. Banuelos E, Ramsey K, Belnap N, Krishnan M, Balak C, Szelinger S, et al. Case report: novel mutations in TBC1D24 are associated with autosomal dominant tonic-clonic and myoclonic epilepsy and recessive parkinsonism, psychosis, and intellectual disability. F1000Res. 2017;6:553.

86. Doummar D, Mignot C, Apartis E, Villard L, Rodriguez D, Chantot-Bastaraud S, et al. A novel homozygous TBC1D24 mutation causing multifocal myoclonus with cerebellar involvement. Mov Disord. 2015;30:1431–2.