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Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy

Synonym: Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE), ADSHE

Hirokazu Kurahashi, MD, PhD[1] and Shinichi Hirose, MD, PhD[2]

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Summary

Clinical characteristics

Autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) is a seizure disorder characterized by clusters of nocturnal motor seizures that are often stereotyped and brief (<2 minutes). They vary from simple arousals from sleep to dramatic, often hyperkinetic events with tonic or dystonic features. Affected individuals may experience an aura. Retained awareness during seizures is common. A minority of individuals experience daytime seizures. Age of onset ranges from infancy to adulthood. About 80% of individuals develop ADSHE in the first two decades of life; mean age of onset is ten years. Clinical neurologic examination is normal and intellect is usually preserved, but reduced intellect, psychiatric comorbidities, or cognitive deficits may occur. Within a family, the manifestations of the disorder may vary considerably. ADSHE is lifelong but not progressive. As an individual reaches middle age, seizures may become milder and less frequent.

Diagnosis/testing

The diagnosis of ADSHE is established in a proband who has suggestive clinical findings and a family history consistent with autosomal dominant inheritance and/or a heterozygous pathogenic variant in *CABP4*, *CHRNA4*, *CHRNA2*, *CHRNB2*, *CRH*, *DEPDC5*, *KCNT1*, *NPRL2*, *NPRL3*, or *STX1B* identified by molecular genetic testing.

Management

Treatment of manifestations: Many anti-seizure medications (ASM) may be effective. Carbamazepine is associated with remission in about 70% of individuals, often in relatively low doses. Individuals with ADSHE associated with the *CHRNA4* pathogenic variant p.Ser284Leu are more responsive to zonisamide than carbamazepine. *KCNT1*-related ADSHE is difficult to treat but may be treatable using quinidine based on limited data. Resistance to ASM is present in about 30% of affected individuals and typically requires a trial of all

Author Affiliations: 1 Aichi Medical University, Nagakute, Japan; Email: kurahashi.hirokazu.736@mail.aichi-med-u.ac.jp. 2 Fukuoka University, Fukuoka, Japan; Email: hirose@fukuoka-u.ac.jp.

appropriate ASM. Adjunctive fenofibrate therapy or vagal nerve stimulation may be considered in individuals resistant to standard ASM.

Surveillance: Reevaluation of EEGs at regular intervals to monitor disease progression, as well as assessment for changes in seizure semiology, changes in tone, and movement disorders; monitoring of developmental progress and educational needs.

Evaluation of relatives at risk: A medical history from relatives at risk can identify those with ADSHE so that treatment can be initiated promptly.

Pregnancy management: Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible.

Genetic counseling

ADSHE, by definition, is inherited in an autosomal dominant manner. Most individuals diagnosed with ADSHE have an affected parent. Each child of an individual with ADSHE has a 50% chance of inheriting the ADSHE-related pathogenic variant; the chance that the offspring will manifest ADSHE is (50% x 70% =) 35%, assuming penetrance of 70%. If the ADSHE-related pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

The International League Against Epilepsy (ILAE) has proposed diagnostic criteria for sleep-related hypermotor (hyperkinetic) epilepsy (SHE) [Riney et al 2022], which consist of three groups of criteria.

Mandatory feature. Brief focal motor seizure with hyperkinetic or asymmetric tonic/dystonic features occurring predominantly during sleep

Alerts. Features that are absent in most cases but rarely can be seen. Their presence should result in caution in diagnosing the syndrome and consideration of other conditions. They include the following:

- Seizures predominantly from the awake state
- Frequent epileptiform abnormality outside of the frontal regions
- Generalized epileptiform abnormality by EEG
- Age at onset younger than ten or older than 20 years
- Moderate-to-severe intellectual disability, or focal neurologic abnormalities on examination

Exclusionary features

- Seizures occur only during wakefulness
- Generalized-onset seizures
- Age at onset younger than two months or older than 64 years

Suggestive Findings

Autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) **should be suspected** in individuals with the following clinical and neuroimaging findings, EEG findings, and family history.

Clinical findings

- Clusters of brief (<2 minutes) motor seizures during sleep that are often stereotyped with abrupt onset and offset. Seizures may include the following:
  - Nightmares

    - Verbalizations
    - Sudden limb movements
- Preserved intellect, although reduced intellect, cognitive deficits, or psychiatric comorbidities may occur
- Normal clinical neurologic examination

Note: The clinical features of ADSHE are indistinguishable from those of nonfamilial SHE (i.e., SHE diagnosed in an individual with a negative family history), the causes of which are unknown but may include *de novo* variants of relevant genes [Hayman et al 1997, Tenchini et al 1999, Steinlein et al 2000, Tinuper et al 2016].

EEG findings

- Interictal EEG may be normal or show infrequent epileptiform discharges.
- Ictal scalp EEG may be normal or obscured by movement artifact.
- Intracranial recordings demonstrate that ictal discharge may arise from various frontal as well as extrafrontal areas.

Neuroimaging findings

- Usually normal in individuals with ADSHE
- Focal cortical dysplasia may be present in some individuals with drug-resistant SHE, especially in individuals with pathogenic variants in GATOR complex genes (e.g., *DEPDC5*, *NPRL2*, *NRPL3*).

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

A clinical diagnosis of ADSHE is **established** in a proband based on the presence of clinical features, EEG findings and family history detailed in Suggestive Findings. A molecular diagnosis of ADSHE is established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in in one of the genes listed in Table 1. A pathogenic variant is identified in 19% of individuals with a family history of SHE and 7% of individuals with a negative family history [Licchetta et al 2020].

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous variant of uncertain significance in any of the genes in Table 1 does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the clinical findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other epilepsy phenotypes are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and EEG findings suggest the diagnosis of ADSHE, molecular genetic testing approaches can include use of a **multigene panel**.

An epilepsy multigene panel that includes *CABP4*, *CHRNA2*, *CHRNA4*, *CHRNB2*, *CRH*, *DEPDC5*, *KCNT1*, *NPRL2*, *NPRL3*, and *STX1B* (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that

do not explain the underlying phenotype. Notes: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other epilepsy phenotypes, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy

Gene [1, 2]	Proportion of ADSHE Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
CABP4	Rare (only 1 pedigree reported) [6, 7]	Rare (only 1 pedigree reported) [6]	
CHRNA2	Rare [6, 8]	Rare [6, 8]	
CHRNA4	2.9% of sporadic cases [6, 8, 9] 6.3% of familial cases [6, 9]	2.9% of sporadic cases [6, 8, 9] 6.3% of familial cases [6, 9]	
CHRNB2	Rare [6, 10]	Rare [6, 10]	
CRH	Rare [6, 11]	Rare [6, 11]	
DEPDC5	3.9% of sporadic cases [6, 9,12] 6.3% of familial cases [6, 9]	2.9% of sporadic cases [6, 8, 9] 6.3% of familial cases [6, 9]	1 person w/intragenic deletion in *DEPDC5* [13]
KCNT1	1.0% [6, 9, 14]	1.0% [6, 9, 14]	
NRPL2	1.0% of sporadic cases [6, 9, 12] 6.3% of familial cases [6, 9]	1.0% of sporadic cases [6, 9, 12] 6.3% of familial cases [6, 9]	
NRPL3	Rare	Rare	
STX1B	Rare (only 1 pedigree reported)	Rare (only 1 pedigree reported)	

Table 1. continued from previous page.

Gene [1, 2]	Proportion of ADSHE Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
Unknown [14]	~90%		

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. Chen et al [2017], Guo et al [2022]
8. Reported in two families [Aridon et al 2006, Conti et al 2015].
9. Licchetta et al [2020]
10. 10%-15% of individuals with a family history have pathogenic variants in subunits of the nicotinic acetylcholine receptor [Ferini-Strambi et al 2012].
11. Combi et al [2005], Sansoni et al [2013]
12. Picard et al [2014]
13. Baldassari et al [2019]
14. Heron et al [2012]

Clinical Characteristics

Clinical Description

Autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) is characterized by clusters of nocturnal motor seizures with a range of manifestations.

Table 2. Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Sleep-related seizures	100%	• Focal motor seizures w/vigorous hyperkinetic or asymmetric tonic/ dystonic features [1] • May occur at any stage during sleep, but typically cluster in non-REM sleep • Some persons experience daytime seizures.
EEG abnormalities	• 10%-50% while awake [1, 2] • 50% during sleep [1, 2]	• Interictal epileptiform abnormalities over the frontal areas during sleep. • Ictal EEG may show evolving sharp- or spike-and-wave, rhythmic slow activity, or diffuse flattening.
Cognitive issues	53% [3]	Some persons have reduced intellect, cognitive deficits, or psychiatric issues.

1. Riney et al [2022]
2. Provini et al [1999]
3. Licchetta et al [2018]

Sleep-related seizures. History may be obtained from the affected individual and witnesses, supplemented if necessary by video EEG monitoring.

Seizures may occur during any stage of sleep, although typically they cluster in non-REM (NREM) sleep, most commonly in stage 2 sleep [Picard & Scheffer 2012]. The affected individual often goes back to sleep rapidly after a seizure, only to be awakened by another event.

Seizures in ADSHE are often stereotyped and brief (<2 minutes); they vary from simple arousals from sleep to dramatic hyperkinetic events with tonic or dystonic features. Subtle and stereotypic motor seizures are accompanied by abrupt recurrent arousals from NREM sleep ("paroxysmal arousals"). The hyperkinetic manifestations may appear bizarre, sometimes with ambulation, bicycling, and a wide range of movements including flinging, throwing the arms, jumping, and pelvic thrusting. Seizures may have greater complexities ("epileptic wandering"). Reported seizure frequency ranges from one to 20 attacks each night, with a mean of 20 seizures per month; about 60% of affected individuals reported more than 15 seizures per month.

Retained awareness during seizures is common and may cause affected individuals to fear falling asleep. Autonomic signs such as tachycardia, tachypnea, and irregular respiratory rhythm are also seen. Focal aware sensory or cognitive seizures, for example, or a sense of difficulty breathing and hyperventilation may precede the motor signs. Focal seizures evolving to bilateral tonic-clonic seizures can also occur.

Some individuals experience an aura preceding the seizure during sleep and are aware of the onset of a seizure. Auras may be nonspecific or may consist of numbness in one limb, fear, a shiver, vertigo, or a feeling of falling or being pushed.

Note: A minority of individuals experience daytime seizures, typically during a period of poor seizure control. Some of the reported seizures are paroxysmal dystonia similar to those during sleep, and others are generalized tonic-clonic seizures, generalized atonic seizures, and focal impaired awareness seizures.

EEG findings

- Ictal EEG recordings may not show definitive ictal patterns, or ictal patterns may be obscured by movement artifact. If present, ictal rhythms may show evolving sharp waves or a spike-and-wave pattern, rhythmic slow activity, or diffuse flattening [Riney et al 2022].
- Interictal waking EEG shows anterior quadrant epileptiform activity in very few affected individuals.
- Interictal sleep EEG shows epileptiform abnormalities over the frontal areas in approximately 50% of affected individuals [Provini et al 1999].

Cognitive findings. Clinical neurologic examination is typically normal and intellect is usually preserved [Oldani et al 1996, Nakken et al 1999]. Several studies have reported that some individuals with SHE have reduced intellect, cognitive deficits, or psychiatric comorbidities [Provini et al 1999, Picard et al 2000, Wood et al 2010, Licchetta et al 2018]. Picard et al [2009] found below-normal general intellect in five (45%) of 11 subjects, with special difficulty in executive tasks, and concluded that cognitive dysfunction is an integral part of ADSHE caused by heterozygous pathogenic variants in the nicotinic acetylcholine receptor (see Phenotype Correlations by Gene).

Licchetta et al [2018] reported 60 individuals with SHE. Of these, 15% had intellectual disability and 53.3% had neuropsychologic deficits. The profile of impairment showed worse verbal IQ, as well as deficits in extrafrontal and selective frontal functions. In addition, individuals with pathogenic variants in ADSHE genes had lower IQ than individuals without pathogenic variants, irrespective of the specific gene.

Familial variation. Within a family, the manifestations of the disorder may vary considerably; individuals with subtle manifestations may not present for medical attention.

A high incidence of true parasomnias has been reported in relatives of individuals with ADSHE [Provini et al 1999]. True parasomnias were distinguished from true seizures based on their age-dependent course, rarity, and

nature of the episodes (episodes typically not violent and often not disturbing for the affected individual). They often ended well before the onset of clear-cut seizures.

Onset and prognosis. ADSHE is lifelong but not progressive. Onset ranges from infancy to adulthood. Most affected individuals develop ADSHE in the first two decades of life, typically in adolescence (age 11-14 years), but age of onset ranges from two months to 64 years [Scheffer et al 1995, Oldani et al 1996, Provini et al 1999, Licchetta et al 2017]. As an individual reaches middle age, attacks may become milder and less frequent. Seizures may vary over time. For example, tonic attacks appearing in early childhood may evolve into seizures with dystonic or hyperkinetic components in later childhood.

Phenotype Correlations by Gene

Table 3. Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy: Phenotype Correlations by Gene

Gene [1]	Phenotypic Feature			
	Epilepsy	Cognitive issues	Other psychiatric & behavioral issues	Penetrance
DEPDC5 [2]	Higher rate of drug resistance, daytime seizures	–	–	–
KCNT1 [3]	More severe, earlier age of onset	More severe	More common	More complete penetrance
STX1B	Peri-ictal hypotension	–	–	–

1. There are no known phenotype correlations for the other ADSHE-associated genes: *CABP4*, *CHRNA2, CHRNA4*, *CHRNB2*, *CRH*, *NPRL2*, and *NPRL3*.
2. Picard et al [2014]
3. Individuals with heterozygous pathogenic variants in *KCNT1* may have these features in comparison to individuals with pathogenic variants in neuronal nicotinic acetylcholine receptor (nAChR) genes (*CHRNA2*, *CHRNA4*, *CHRNB2*) [Heron et al 2012].

Genotype-Phenotype Correlations

Steinlein et al [2012] suggested that certain pathogenic variants in nicotinic acetylcholine receptor (nAChR) genes (*CHRNA2*, *CHRNA4*, *CHRNB2)* may be associated with an increased risk of unfavorable outcomes.

Individuals with the *CHRNA4* pathogenic variant p.Ser284Leu tend to have early onset of epilepsy and less favorable cognitive function. They respond only partially to carbamazepine and are more responsive to zonisamide [Provini et al 1999, Ito et al 2000, Combi et al 2004].

The *CHRNB2* pathogenic variant p.Ile312Met was associated with clinically relevant deficits in cognitive function. Affected members from two unrelated families with the variant show normal or low-average intellect with moderate-to-significant verbal memory deficits [Bertrand et al 2005, Cho et al 2008].

Marked intrafamilial variation in severity is seen in ADSHE; the reasons for this are not well understood.

Penetrance

The penetrance of ADSHE is estimated to be 70%. *KCNT1*-related ADSHE demonstrates complete penetrance compared to 60%-80% in nAChR-related ADSHE.

Nomenclature

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is now referred to as autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) [Tinuper et al 2016, Riney et al 2022].

The term "nocturnal" implies a chronobiological pattern of seizure occurrence, whereas occurrence in sleep (rather than at night) is the most important characteristic of the epilepsy in ADSHE. The characteristic seizures that consist of hypermotor manifestations can arise from other cerebral regions in addition to the frontal lobe [Tinuper et al 2016]. The ILAE task force notes that "hyperkinetic" rather than "hypermotor" is the currently accepted term for the focal motor seizures with vigorous movements that can be seen in this syndrome [Riney et al 2022].

Prevalence

The number of families with ADSHE reported to date exceeds 100 [Picard & Brodtkorb 2007]. The estimated prevalence of SHE in the adult population is estimated to be 1.8-1.9 in 100,000 [Vignatelli et al 2017].

Genetically Related (Allelic) Disorders

No mendelian phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CHRNA4*, *CHRNB2*, or *CRH*.

Other phenotypes associated with pathogenic variants in *CABP4*, *CHRNA2*, *DEPDC5*, *KCNT1*, *NPRL2*, *NPRL3*, and *STX1B* are listed in Table 4.

Table 4. Allelic Disorders

Gene	Disorder(s)	*GeneReview* / Reference
CABP4 [1]	• Cone rod dystrophy • Retinitis pigmentosa • Leber congenital amaurosis	Leber Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy Overview; Khan et al [2013]
CHRNA2	Benign familial infantile seizures	Trivisano et al [2015]
DEPDC5	• Familial focal epilepsies incl familial temporal lobe epilepsy & familial focal epilepsy w/variable foci • Rolandic epilepsy, unclassified focal childhood epilepsy, & focal epilepsy w/cortical dysplasia	*DEPDC5*-Related Epilepsy
KCNT1	• Epilepsy of infancy w/migrating focal seizures • Less common seizure phenotypes incl infantile spasms, Ohtahara syndrome, early myoclonic encephalopathy, leukodystrophy &/or leukoencephalopathy, focal epilepsy, & multifocal epilepsy	*KCNT1*-Related Epilepsy
NPRL2	• Familial focal epilepsy w/variable foci • Infantile spasms	Ricos et al [2016], Baldassari et al [2019]
NPRL3	Familial focal epilepsy w/variable foci	Ricos et al [2016]
STX1B	Fever-assoc epilepsy syndromes	Schubert et al [2014]

1. Biallelic variants are associated with retinal disease.

Differential Diagnosis

The differential diagnosis of autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) includes autosomal recessive SHE caused by biallelic pathogenic variants in *PRIMA1* (reported in only one family to date [Hildebrand et al 2015]) and other conditions of varied etiology, including the following:

- **Other focal seizures occurring predominantly from sleep** but not having the hyperkinetic or asymmetric tonic/dystonic features, which are characteristics of ADSHE
- **Normal sleep** is characterized by periodic arousals, and occasionally other sleep-related movements or phenomena including nightmares.

- **Parasomnias** (disorders in which undesirable physical and mental phenomena occur mainly or exclusively during sleep [American Academy of Sleep Medicine 2014]) including the following may be considered:
  - ***Pavor nocturnus* (night terrors),** a common childhood syndrome, is characterized by attacks of extreme fear and distress that occur one or two hours after the child falls asleep. The child is unaware during the attack, which lasts five to ten minutes, and is amnesic for the event the following day [Schenck & Mahowald 2000].
  - **Benign somnambulism (sleepwalking)** is not accompanied by abnormal motor behavior or dystonia and is usually a self-limiting disorder of childhood. Somnambulism is often familial.
- **Hysteria** is often considered in the differential diagnosis because the individual retains awareness during the attacks, which can be bizarre. Clues to the organic nature of attacks are the occurrence during sleep and the stereotyped semiology (i.e., sequence of observed events during the attack).
- **Periodic limb movement disorder (nocturnal myoclonus)** affects the flexor muscles of the lower limbs and is characterized by segmental motor activity in muscles that recurs every 20-30 seconds. Brief stationary movements may be followed by myoclonic or repetitive clonic jerks that coincide with the periodic K-complexes of light sleep.
- **Restless legs syndrome** is often accompanied by segmental motor activity and may be a spinal cord-mediated disorder.
- **REM sleep disorders** may include prominent motor and verbal manifestations that are often of unknown cause or secondary to other neurologic disorders. REM sleep disorders typically occur in men ages 55-60 years. Polysomnography is a useful diagnostic tool.
- **Respiratory disorders** such as asthma may be considered because of difficulty breathing.
- **Obstructive sleep apnea** may be considered in individuals complaining of daytime sleepiness who are not aware of their nocturnal attacks.

Management

No clinical practice guidelines regarding the management for autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ADSHE, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy

System/Concern	Evaluation	Comment
Neurologic	Assessment by neurologist w/eval of suspected seizures as indicated	To incl EEG & high-resolution brain MRI to evaluate for focal brain malformations, if suspected based on seizure semiology
Development	Assessment by developmental specialist	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric	Assessment by psychiatrist	For any psychiatric comorbidities or complications
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of ADSHE to facilitate medical & personal decision making

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADSHE = autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Treatment of Manifestations in Individuals with Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Standardized treatment w/ASM by epileptologist or experienced neurologist	• Many ASM may be effective; In about 70% of persons w/ADSHE, carbamazepine is assoc w/remission of seizures, often w/relatively low doses. However, persons w/ADSHE assoc w/*CHRNA4* pathogenic variant p.Ser284Leu respond only partially to carbamazepine & are more responsive to zonisamide. [1] • *KCNT1*-related ADSHE is difficult to treat. Some persons w/EIMFS caused by pathogenic variants in *KCNT1* & treated w/quinidine were noted to have marked reduction in seizure frequency. [2] Therefore, quinidine may be considered for treatment of *KCNT1*-related ADSHE, though data regarding its efficacy are limited. • Resistance to ASM occurs in ~30% of affected persons. Intrafamilial variation in pharmacoresponsiveness occurs; therefore, all appropriate ASMs should be tried. • Adjunctive therapy w/fenofibrate ↓ seizure frequency in persons w/pharmacoresistant ADSHE in 1 study. [3] • Surgical treatment is effective in persons w/FCD-assoc SHE. • Education of parents/caregivers is recommended. [4]
	Vagal nerve stimulation	May be considered in persons w/epilepsy who are resistant to ASM. [5]
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Psychiatric issues	Standardized treatment by psychiatrist	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for support

ADSHE = autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy; ASM = anti-seizure medication; EIMFS = epilepsy of infancy with migrating focal seizures; FCD = focal cortical dysplasia
1. Provini et al [1999], Ito et al [2000], Combi et al [2004]
2. Bearden et al [2014]
3. Puligheddu et al [2017]
4. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.
5. Carreño et al [2010]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Caregivers

For information on nonmedical interventions and coping strategies for parents or caregivers of children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Recommended Surveillance for Individuals with Autosomal Dominant Sleep-related Hypermotor Epilepsy (ADSHE)

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as new seizure types, changes in tone, & movement disorders.	At each visit
Development	Monitor developmental progress & educational needs.	If applicable
	Eval by developmental pediatrician or developmental specialist	Annually &/or as needed
Psychiatric	Eval by psychiatrist for any psychiatric comorbidities	If applicable
Family/Community	Assess family need for social work support (e.g., palliative/respite care, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment. Evaluations can include one of the following:

- If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, a medical history to seek evidence of affected status should be elicited from relatives at risk.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In general, women with epilepsy or a seizure disorder from any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASM may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy during which the medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated

with exposure to an untreated maternal seizure disorder. Therefore, use of ASM to treat a maternal seizure disorder during pregnancy is typically recommended.

Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE) is inherited in an autosomal dominant manner.

PRIMA1-related SHE, which is inherited in an autosomal recessive manner, was reported in only one family [Hildebrand et al 2015].

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with ADSHE have an affected parent.
- A proband may have the disorder as the result of a *de novo* ADSHE-related pathogenic variant.
- Recommendations for the evaluation of parents of a child with SHE and no known family history of SHE include:
  - A detailed clinical and family history;
  - Molecular genetic testing (if a molecular diagnosis has been established in the proband).
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with ADSHE may appear to be negative because of failure to recognize the disorder in family members or reduced penetrance. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluations of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the ADSHE-related pathogenic variant identified in the proband).

Sibs of a proband. The risk to sibs of a proband depends on the clinical and genetic status of the parents:

- If one parent has phenotypic features of ADSHE and/or is known to have an ADSHE-related pathogenic variant, the risk to each sib of inheriting the pathogenic variant is 50%. The chance that the sib will manifest ADSHE is (50% x 70% =) 35%, assuming an estimated penetrance of 70%. (Note: *KCNT1*-related ADSHE demonstrates complete penetrance.)

  Within a family, the manifestations of ADSHE in affected individuals may vary considerably.
- If the proband has a known ADSHE-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband

- Each child of an individual with ADSHE has a 50% chance of inheriting the ADSHE-related pathogenic variant.
- The chance that the offspring will manifest ADSHE is (50% x 70% =) 35%, assuming penetrance of 70%.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected with ADSHE or has an ADSHE-related pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Other genetic counseling issues. Individuals may not be aware of the significance of their attacks; in some families, individuals may be reluctant to reveal their symptoms [Picard & Scheffer 2012].

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.
- Discussion of the risks and benefits of using a given anti-seizure medication during pregnancy should ideally take place before pregnancy (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

If the ADSHE-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Because ADSHE is associated with intrafamilial clinical variability and reduced penetrance, the prenatal identification of an ADSHE-related pathogenic variant cannot be used to reliably predict future clinical manifestations.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Epilepsy Society**
  www.aesnet.org
- **Canadian Epilepsy Alliance**
  Canada
  Phone: 1-866-EPILEPSY (1-866-374-5377)
  www.canadianepilepsyalliance.org
- **Epilepsy Foundation**
  Phone: 301-459-3700
  Fax: 301-577-2684
  www.epilepsy.com
- **National Institute of Neurological Disorders and Stroke (NINDS)**
  Phone: 800-352-9424 (toll-free); 301-496-5751; 301-468-5981 (TTY)
  Epilepsy Information Page

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CABP4	11q13.2	Calcium-binding protein 4	CABP4 database	CABP4	CABP4
CHRNA2	8p21.2	Neuronal acetylcholine receptor subunit alpha-2	CHRNA2 database	CHRNA2	CHRNA2
CHRNA4	20q13.33	Neuronal acetylcholine receptor subunit alpha-4	CHRNA4 database	CHRNA4	CHRNA4
CHRNB2	1q21.3	Neuronal acetylcholine receptor subunit beta-2	CHRNB2 database	CHRNB2	CHRNB2
CRH	8q13.1	Corticoliberin	CRH database	CRH	CRH
DEPDC5	22q12.2-q12.3	GATOR1 complex protein DEPDC5		DEPDC5	DEPDC5
KCNT1	9q34.3	Potassium channel subfamily T member 1		KCNT1	KCNT1
NPRL2	3p21.31	GATOR complex protein NPRL2		NPRL2	NPRL2

Table A. continued from previous page.

NPRL3	16p13.3	GATOR complex protein NPRL3		NPRL3	NPRL3
STX1B	16p11.2	Syntaxin-1B		STX1B	STX1B

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy (View All in OMIM)

118502	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 2; CHRNA2
118504	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 4; CHRNA4
118507	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 2; CHRNB2
122560	CORTICOTROPIN-RELEASING HORMONE; CRH
600513	EPILEPSY, NOCTURNAL FRONTAL LOBE, 1; ENFL1
600928	NITROGEN PERMEASE REGULATOR-LIKE 3; NPRL3
601485	SYNTAXIN 1B; STX1B
603204	EPILEPSY, NOCTURNAL FRONTAL LOBE, 2; ENFL2
605375	EPILEPSY, NOCTURNAL FRONTAL LOBE, 3; ENFL3
607072	NPR2-LIKE PROTEIN, GATOR1 COMPLEX SUBUNIT; NPRL2
608167	POTASSIUM CHANNEL, SUBFAMILY T, MEMBER 1; KCNT1
608965	CALCIUM-BINDING PROTEIN 4; CABP4
614191	DEP DOMAIN-CONTAINING PROTEIN 5; DEPDC5
615005	EPILEPSY, NOCTURNAL FRONTAL LOBE, 5; ENFL5

Molecular Pathogenesis

Pathogenic variants in (1) genes encoding subunits of the neuronal nicotinic acetylcholine receptor (nAChR) (*CHRNA4*, *CHRNB2*, *CHRNA2*); (2) genes encoding components of GATOR1 (*DEPDC5*, *NPRL2*, *NPRL3*); and (3) *KCNT1*, *CRH*, *CABP4*, and *STX1B* are known to cause autosomal dominant sleep-related hypermotor (hyperkinetic) epilepsy (ADSHE).

Genes encoding subunits of the neuronal nicotinic acetylcholine receptor (nAChR)

- ***CHRNA4***, encoding the alpha-4 subunit of the neuronal nicotinic acetylcholine receptor (nAChR)
- ***CHRNB2***, encoding the beta-2 subunit of the nAChR
- ***CHRNA2***, encoding the alpha-2 subunit of the nAChR

The nAChR is a heterologous pentamer comprising various combinations of alpha and beta subunits, encoded by *CHRNA2-CHRNA7* and *CHRNB2-CHRNB4*, respectively. The most common configuration in the thalamus and the cortex is $(\alpha\text{-}4)_2(\beta\text{-}2)_3$ subunits (i.e., 2 α-4 and 3 β-2 subunits). The nicotinic acetylcholine receptor is widely distributed in the brain, including the frontal lobes. It is thought that the receptor is a presynaptic modulator of other neurotransmitter systems, including gamma-amino butyric acid (GABA), glutamate, and dopamine, and therefore may have variable effects on excitatory and inhibitory pathways [Kuryatov et al 1997, Bertrand 1999, Buisson et al 1999, Picard et al 1999].

Each nAChR subunit has a conserved N-terminal extracellular domain followed by three conserved transmembrane domains, a variable cytoplasmic loop, a fourth conserved transmembrane domain, and a short C-terminal extracellular region [Elliott et al 1996]. The α subunits are characterized by the presence of a pair of

cysteine residues (Cys161 and Cys175, NP_000735.1) presumed to function as part of the acetylcholine binding site when the α-4 subunits are complexed as a heterologous pentamer with the β subunits [Figl et al 1998]. *CHRNB2* is similar to *CHRNA4*, but the β subunits encoded by the genes are defined by the lack of paired cysteine residues [Elliott et al 1996]. The second transmembrane domain of the receptor forms the ion channel pore and is the site of most of the pathogenic variants implicated in ADSHE.

Pathogenic variants in *CHRNA4*, *CHRNA2*, and *CHRNB2* associated with ADSHE occur in highly conserved amino acids and alter the function of the resulting receptors. Functional studies of different pathogenic variants provide conflicting results, although an increase in in vitro acetylcholine sensitivity is typical for known ADSHE-associated pathogenic variants [Kuryatov et al 1997, Steinlein et al 1997, Bertrand et al 1998, Bertrand 1999, De Fusco et al 2000, Phillips et al 2001, di Corcia et al 2005]; thus, the mechanism whereby pathogenic variants cause ADSHE is poorly understood, though increased receptor sensitivity to acetylcholine and gain of function of nAChR may be a contributing mechanism [Aridon et al 2006, Hoda et al 2009]. Carbamazepine and oxcarbazepine produce a noncompetitive channel inhibition in heteromeric neuronal nicotinic receptors including mutated α-2 subunits as well as wild type α-2 subunits, but the different heteromeric nicotinic receptors exhibit distinct pharmacologic properties [Di Resta et al 2010].

Genes encoding components of GATOR1

- ***DEPDC5***, encoding dishevelled, egl-10, and pleckstrin (DEP) domain-containing protein 5
- ***NPRL2***, nitrogen permease regulator-like 2
- ***NPRL3***, nitrogen permease regulator-like 3

DEPDC5 is a component of GATOR1 (GTPase-activating protein [GAP] *a*ctivity *to*ward *R*ags complex 1), which negatively regulates mTORC1 (mammalian target of rapamycin complex 1) [Bar-Peled et al 2013] and is expressed ubiquitously in human tissues. The mTOR pathway plays a role in many activities including cell growth, cell proliferation, and metabolism. Most pathogenic variants in *DEPDC5* are truncating variants that can be expected to result in nonsense-mediated mRNA degradation. Pathogenic variants in *DEPDC5* appear to have a less dramatic effect on mTORC1 signaling but disturb it sufficiently to cause focal epilepsy. Indeed, the phenotype of individuals with *DEPDC5* pathogenic variants has expanded with the identification of variants associated with Rolandic epilepsy, unclassified focal epilepsy [Lal et al 2014], and focal epilepsy with brain malformations [Scheffer et al 2014]. NPRL2 and NPLR3 are also components of GATOR1, and pathogenic variants in these genes have been reported in ADSHE and sporadic SHE, as well as other focal epilepsies [Ricos et al 2016].

KCNT1. *KCNT1* (previously known as *SLACK*, *SLO2.2*, and *KCa4.1*) encodes a sodium-activated potassium channel [Joiner et al 1998]. The sodium-activated potassium channel encoded by *KCNT1* is widely distributed in many regions of the mammalian brain, including the frontal cortex. Its activity contributes to the slow hyperpolarization that follows repetitive firing. The KCNT1 channel contains six putative membrane-spanning regions and an extended C-terminus. The C-terminal cytoplasmic domain contains several motifs believed to interact with a protein network. One of the proteins is fragile X mental retardation protein (FMRP), a potent stimulator of KCNT1 channel activity [Brown et al 2010]. All identified pathogenic variants to date are located within the intracellular region, and most alter amino acids within or immediately adjacent to a nicotinamide adenine dinucleotide (NAD+)-binding site. Mutated channels with pathogenic variants identified in ADSHE produce voltage-activated currents with higher magnitude compared to wild type, leading to gain of function. However, the mechanisms underlying increased neuronal excitability due to a gain of function of KCNT1 channels are not known.

CRH. *CRH* encodes corticotropin-releasing hormone (CRH), which is widely distributed throughout the central nervous system; it acts as a neurotransmitter or neuromodulator in extrahypothalamic circuits to integrate a multisystem response to stress that controls numerous behaviors including sleep and arousal. Variations in the

promoter [Combi et al 2005] or in the pro-sequence region [Sansoni et al 2013] have been reported. The variant identified in one family with ADSHE decreases peptide secretion in vitro [Sansoni et al 2013].

CABP4. *CABP4* encodes the calcium-binding protein 4 (CABP4), which belongs to the family of neuronal Ca^{2+}-binding proteins and shares structural homology with calmodulin. It has been shown to modulate voltage-dependent Ca^{2+} channels. Pathogenic variants in *CABP4* have been identified in individuals with retinal diseases. Missense variant c.464G>A (p.Gly155Asp) was identified in seven affected individuals from a four-generation ADSHE pedigree [Chen et al 2017]. The mechanisms by which pathogenic variants in this gene cause ADSHE are still unclear; the missense variant noted above was associated with reduced expression of CABP4 proteins in vitro [Guo et al 2022].

STX1B. *STX1B*, encoding syntaxin-1B, is involved in the release of glutamate and GABA and plays a role in the regulation of fast synaptic vesicle exocytosis [Mishima et al 2014]. *STX1B* pathogenic variants have been identified in individuals with fever-associated epilepsy syndromes [Schubert et al 2014]. In one study, multigene panel testing revealed a likely pathogenic variant c.106-2A>G in an individual with SHE [Peres et al 2018]. Seizures in this individual were accompanied by autonomic features evidenced by significant peri-ictal hypotension. This splice site variant is predicted to abolish the native splicer acceptor site, leading to aberrant splicing resulting in abnormal protein or nonsense-mediated mRNA decay.

Mechanism of disease causation

- *CHRNA2*, *CHRNA4*, *CHRNB2*, *KCNT1*. Likely gain of function
- *DEPDC5*, *NPRL2*, *NPRL3*, *STX1B*. Loss of function (haploinsufficiency)
- *CRH*. The direct role in the pathogenesis of SHE is still unclear, but alteration of hormone levels may be associated.
- *CABP4*. The direct role in the pathogenesis of SHE is still unclear, but reduction of the expression of CABP4 may be associated.
- *STX1B*. The direct role in the pathogenesis of SHE is still unclear; loss of function of STX1B leads to impairment of regulation of synaptic vesicle exocytosis, which may cause SHE.

Table 8. Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy: Gene-Specific Laboratory Considerations

Gene [1]	Special Consideration
CABP4	Only 1 variant, c.464G>A, has been reported.
CHRNA2 [2]	Located w/in transmembrane 1 & 2
CHRNA4 [2]	Mainly located w/in transmembrane 2
CRHNB2 [2]	Mainly located w/in transmembrane 2 & 3
CRH	Only has 2 exons, & the 1st is noncoding. Variants in promotor region (e.g., c.-365G>C, c.-669C>A [3]) have been identified in ADSHE that may not be detected by standard exome sequencing.
DEPDC5 [4]	Pathogenic variants are located in protein-coding region.
KCNT1 [5]	Variants identified in persons w/ADSHE cluster in regulators of potassium (RCK) domains of channel protein.
NPRL2 [4]	Pathogenic variants are located throughout protein-coding region.
NPRL3 [4]	Pathogenic variants are located throughout protein-coding region.

1. Genes from Table 1 in alphabetic order.
2. Bisulli et al [2019]
3. Combi et al [2005]
4. Ricos et al [2016]
5. See *KCNT1*-Related Epilepsy.

Table 9. Autosomal Dominant Sleep-Related Hypermotor (Hyperkinetic) Epilepsy: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
CABP4	NM_145200.5 NP_660201.1	c.464G>A	p.Gly155Asp	Variant specifically assoc w/ADSHE [Chen et al 2017]
CHRNA4	NM_000744.7 NP_000735.1	c.851C>T	p.Ser284Leu	Assoc w/early-onset epilepsy & less favorable cognitive function. Persons respond only partially to carbamazepine & are more responsive to zonisamide. [2]
CHRNB2	NM_000748.3 NP_000739.1	c.936C>G	p.Ile312Met	Clinically relevant deficits in cognitive functions, esp in verbal memory [3]
STX1B	NM_052874.5 NP_443106.1	c.106-2A>G	p.?	Reported in 1 person w/sleep-related epilepsy. Seizures accompanied by autonomic features. Variant is predicted to abolish native splicer acceptor site, leading to aberrant splicing resulting in abnormal protein or nonsense-mediated mRNA decay. [4]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Genes from Table 1 are in alphabetic order.

2. Provini et al [1999], Ito et al [2000], Combi et al [2004]

3. Bertrand et al [2005]

4. Peres et al [2018]

Chapter Notes

Author History

Judith Adams, MBBS, FRACP; University of Melbourne (2002-2004)
Samuel F Berkovic, MD, FRACP; Epilepsy Research Institute (2002-2010)
Shinichi Hirose, MD, PhD (2010-present)
Hirokazu Kurahashi, MD, PhD (2010-present)
Ingrid E Scheffer, MBBS, FRACP, PhD; Austin and Repatriation Medical Centre (2002-2010)

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