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Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

[*ADNFLE*]

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Summary

Disease characteristics. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is characterized by clusters of nocturnal motor seizures, which are often stereotyped and brief (five seconds to five minutes in duration). They vary from simple arousals from sleep to dramatic, often bizarre, hyperkinetic events with tonic or dystonic features. Affected individuals may experience aura. Retained awareness during seizures is common. A minority of individuals experience daytime seizures. Onset ranges from infancy to adulthood. About 80% of individuals develop ADNFLE in the first two decades of life, with a mean age of ten years. Neurologic examination is normal and intellect is usually preserved. Within a family, the manifestations of the disorder may vary considerably. ADNFLE is lifelong but not progressive. As an individual reaches middle age, attacks may become milder and less frequent.

Diagnosis/testing. The diagnosis of ADNFLE is made on clinical grounds. A detailed history from the affected individual and witnesses, supplemented if necessary by video-EEG monitoring, is the key to diagnosis. Molecular genetic testing reveals mutations in *CHRNA4* or *CHRNB2* in ~20-30% of individuals with a positive family history and <5% of individuals with a negative family history. Such testing is available on a clinical basis.

Genetic counseling. ADNFLE is inherited in an autosomal dominant manner. Most individuals diagnosed with ADNFLE have an affected parent. The proportion of cases caused by *de novo* gene mutations is unknown, as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient. Penetrance is estimated to be 70%. The risk to each offspring of inheriting the mutant allele is 50%. The chance that the offspring will manifest ADNFLE is (50%)(70%)=35%, assuming penetrance of 70%. Prenatal testing may be available through laboratories offering custom prenatal testing.

Diagnosis

Clinical Diagnosis

- A detailed history from the affected individual and witnesses, supplemented if necessary by video-electroencephalogram (EEG) monitoring, is the key to diagnosis.

History may include nightmares, verbalizations, sudden limb movements or other parasomnias.

- Investigations such as ictal EEG and neuroimaging (to exclude occult pathology) should be performed [Scheffer et al 1995, Oldani et al 1996, Mochi et al 1997, Thomas et al 1998, Nakken et al 1999, De Fusco et al 2000, Picard et al 2000].
- Interictal waking EEG shows anterior quadrant epileptiform activity in very few affected individuals. Sleep recordings may identify interictal activity, but, if present, epileptiform discharges are usually infrequent.
- Ictal EEG recordings may be normal or may be obscured by movement artifact. Ictal rhythms, if present, usually take the form of sharp waves or repetitive 8-11 Hz spikes. Recruiting patterns and rhythmic theta, either bifrontal or unilateral frontal, or with diffuse desynchronization, are occasionally seen [Scheffer et al 1995, Steinlein et al 1997, Oldani et al 1998, Provini et al 1999, Picard et al 2000].
- Cerebral MRI is normal.
- One or more family members are affected; family history is consistent with autosomal dominant inheritance.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. *CHRNA4* and *CHRNB2*, encoding respectively the α4 and ß2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR), are known to be associated with ADNFLE [Steinlein et al 1995, Steinlein et al 1997, Hirose et al 1999, Saenz et al 1999, Gambardella et al 2000, Phillips et al 2000, Steinlein et al 2000, Diaz-Otero et al 2001, Phillips et al 2001, Cho et al 2003, Rozycka et al 2003].

Locus

- A potential ADNFLE locus has been mapped in one family to chromosome 15q24, which is close to the sites of the genes encoding the α3, α5, and ß4 subunits of the nAChR *(CHRNA3*, *CHRNA5*, *CHRNB4*) cluster.
- In other families, linkage has not been established to *CHRNA4*, *CHRNB2*, or the 15q24 locus, suggesting the existence of additional genes associated with ADNFLE [Phillips et al 1998, Tenchini et al 1999, Cho et al 2003].
- Absence of linkage to nine other neuronal nicotinic acetylcholine receptor subunit genes expressed in brain was demonstrated in four unrelated Italian families [Bonati et al 2002].

Molecular genetic testing: Clinical use

- Diagnostic testing

Molecular genetic testing: Clinical method

- **Sequence analysis** of the *CHRNA4* and *CHRNB2* genes identifies mutations in approximately 20-30% of individuals with a positive family history and <5% of individuals who have no other family members with ADNFLE.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Test Method	Mutations Detected	Mutation Detection Rate [1]		Test Availability
		Positive Family History	Negative Family History	
Sequence analysis	*CHRNA4*	~20-30%	<5%	Clinical Testing
	CHRNB2			

1. As reported by laboratories in the GeneTests Laboratory Directory (June 2004)

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Clinical Description

ADNFLE is characterized by clusters of nocturnal motor seizures with a range of manifestations. They are often stereotyped and brief (five seconds to five minutes in duration) [Scheffer et al 1995, Oldani et al 1996, Thomas et al 1998, Nakken et al 1999, Provini et al 1999, Ito et al 2000, Picard et al 2000]. They vary from simple arousals from sleep to dramatic hyperkinetic events with tonic or dystonic features. Various subclassifications of the seizure types have been proposed based on clinical features of the seizures (semiology) and their duration [Montagna et al 1990, Montagna 1992, Sforza et al 1993, Oldani et al 1998, Provini et al 1999]. The hyperkinetic manifestations may appear bizarre, sometimes with ambulation, bicycling movements, ballism (flinging or throwing arm movements), and pelvic thrusting movements. Affected individuals may experience an aura, which may be nonspecific or may consist of fear, a shiver, vertigo, or a feeling of falling or being pushed. Retained awareness during seizures is common and may cause affected individuals to fear falling asleep. Individuals often experience a sense of difficulty breathing and may hyperventilate. Vocalization, clonic features, urinary incontinence, and secondary generalization may occur. Seizures may occur in any stage of sleep [Oldani et al 1996, Steinlein et al 1997, Provini et al 1999], although typically in clusters in non-REM sleep, most commonly in stage two sleep [Scheffer et al 1995, Oldani et al 1998, Provini et al 1999]. A minority of individuals experience daytime seizures, occurring typically during a period of poor seizure control. The affected individual often goes back to sleep rapidly after a seizure, only to be awakened by another event.

Onset ranges from infancy to adulthood. About 80% of affected individuals develop ADNFLE in the first two decades of life [Scheffer et al 1995, Oldani et al 1998, Picard et al 2000], with a mean age of ten years. Neurologic examination is normal and intellect is usually preserved [Oldani et al 1996, Nakken et al 1999]; however, in some individuals, neuropsychological assessment reveals subtle frontal deficits [Picard et al 2000] and reduced intellect [Provini et al 1999]. Families with coexistent intellectual disability have been described [Khatami et al 1998, Cho et al 2003]. A high incidence of true parasomnias (disorders in which undesirable phenomena occur mainly or only during sleep) has been reported in relatives of those with ADNFLE by Provini et al (1999). Within a family, the manifestations of the disorder may vary considerably [Scheffer et al 1995, Hayman et al 1997]; individuals with subtle manifestations may not present for medical attention. Magnusson et al (2003) reported an increase in psychiatric symptoms in families with ADNFLE.

ADNFLE is lifelong but not progressive. As an individual reaches middle age, attacks may become milder and less frequent [Scheffer et al 1995]. Some variability in seizure manifestations may occur over time; for example, tonic attacks appearing in early childhood may evolve into seizures with dystonic or hyperkinetic components in later childhood.

The clinical features in individuals with ADNFLE are indistinguishable from nonfamilial nocturnal frontal lobe epilepsy [Scheffer et al 1995, Hayman et al 1997, Tenchini et al 1999, Steinlein et al 2000]. The term ADNFLE should not be applied unless a known family history of the disorder exists.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been consistently identified. Marked intrafamilial variation in severity is seen, the reasons for which are unknown [Scheffer et al 1995].

Penetrance

Penetrance is estimated to be 70%.

Anticipation

Anticipation has not been observed.

Prevalence

No accurate data concerning the prevalence of ADNFLE exist. Families with the disorder have been identified in many countries including Australia, Canada, France, Germany, Great Britain, Italy, Japan, Korea, Norway, and Spain [Lugaresi & Cirignotta 1981, Scheffer et al 1995, Khatami et al 1998, Oldani et al 1998, Thomas et al 1998, Hirose et al 1999, Nakken et al 1999, Saenz et al 1999, Ito et al 2000, Diaz-Otero et al 2001, Phillips et al 2001, Cho et al 2003]. It is probable that the disorder is underdiagnosed or misdiagnosed in some cases.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The differential diagnosis of the attacks includes an array of conditions of varied etiology.

- Normal sleep is characterized by periodic arousals, and occasionally other sleep-related movements or phenomena such as nightmares may be diagnosed when in fact the diagnosis is ADNFLE [Scheffer et al 1994, Phillips et al 1998].
- Other parasomnias may need to be considered in the differential diagnosis. Parasomnias are disorders in which undesirable physical and mental phenomena occur mainly or exclusively during sleep [American Sleep Disorders Association 1997]. The common childhood syndrome of *pavor nocturnus* (night terrors) 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 (sleep walking) is not accompanied by abnormal motor behavior or dystonia and is usually a self-limiting disorder of childhood. Somnambulism is often familial.
- The seizures of ADNFLE can sometimes be misdiagnosed as hysteria because the individual retains awareness during the attacks, which can appear bizarre. Clues to the organic nature of attacks are the occurrence during sleep and the stereotyped semiology (sequence of observed events during the attack) [Vigevano & Fusco 1993, Scheffer et al 1995].
- Difficulty breathing in ADNFLE may raise the question of respiratory disorders such as asthma [Scheffer et al 1995]. Obstructive sleep apnea may occasionally cause

diagnostic confusion, as some individuals with ADNFLE complain of daytime sleepiness and may not be aware of their attacks.

- Familial dyskinesias, such as paroxysmal dystonic choreoathetosis (PDC) and paroxysmal kinesigenic choreoathetosis (PKC), are rare disorders. In PDC, the attacks typically last five minutes to several hours and occur during the day. Attacks are usually precipitated by ingestion of substances such as alcohol or caffeine and by other stressors. In PKC, the episodes are brief and occur while awake. Attacks are triggered by movement, muscular effort, and startle [Mount et al 1940, Lance 1977, Buruma et al 1986, Byrne et al 1991, Demirkiran & Jankovic 1995].
- Movement disorders occurring during sleep, such as restless legs syndrome and periodic limb movement disorder (also known as nocturnal myoclonus), may be confused with ADNFLE. 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. There may be brief stationary movements followed by myoclonic or repetitive clonic jerks that coincide with the periodic K-complexes of light sleep. Restless legs syndrome is also often accompanied by segmental motor activity and may be a spinal cord- mediated disorder [Demirkiran & Jankovic 995].
- REM sleep disorders may present with prominent motor and verbal manifestations that occur during REM sleep; polysomnography is useful as a diagnostic tool. The condition may be idiopathic or secondary to other neurological disorders, and typically occurs in men ages 55-60 years [Demirkiran & Jankovic 1995]. Thus, there is not a lifelong history of the brief stereotyped events that characterize ADNFLE.
- Another hereditary partial epilepsy syndrome in which some family members may have frontal lobe epilepsy with a nocturnal pattern is familial partial epilepsy with variable foci (FPEVF) [Phillips et al 1998, Steinlein 1999]. FPEVF is distinguished by other family members having partial epilepsy emanating from other cortical regions.

Management

Treatment of Manifestations

- The drug of choice for ADNFLE is carbamazepine, although no controlled trials have been conducted. However, Picard et al (1999) have conducted studies on mutated nAChR that demonstrate an increased sensitivity to carbamazepine compared to wild type receptors. Reports indicate that 70% of affected individuals have remission of seizures with carbamazepine, often with relatively low doses. No trials have looked for differing effects of carbamazepine or other anti-epileptic drugs among the families with different mutations of the nAChR subunit genes, but response rates to medications appear similar in the published literature.
- Drug resistance to anticonvulsants occurs in about 30% of affected individuals. There is intrafamilial variation in pharmacoresponsiveness; however, all appropriate agents should be tried. No controlled trials of drugs that affect cholinergic transmission have been published.

Testing of Relatives at Risk

A medical history to seek evidence of affected status should be elicited from relatives at risk so that treatment can be initiated if appropriate.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Autosomal dominant nocturnal frontal lobe epilepsy is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with ADNFLE have an affected parent.
- However, a proband with ADNFLE may have the disorder as the result of a *de novo* gene mutation or may have another form of nocturnal frontal lobe epilepsy. The proportion of cases caused by *de novo* gene mutations is unknown, as the frequency of subtle signs of the disorder in parents has not been thoroughly evaluated and molecular genetic data are insufficient.
- Recommendations for the evaluation of parents of a child with nocturnal frontal lobe epilepsy and no known family history of NFLE include a detailed clinical and family history. Penetrance is estimated to be 70%. In simplex cases (individuals with no known family history of NFLE), the data on heritability are incomplete; in one report a mother with a *de novo* mutation passed the condition on to her son [Phillips et al 2000].

Sibs of a proband. The risk to sibs and offspring of a proband depends upon the genetic status of the parents.

- If one parent has phenotypic features of ADNFLE or is known to have a disease-causing mutation, the risk to each sib of inheriting the mutant allele is 50%. The chance that the sib will manifest ADNFLE is (50%)(70%) = 35%, assuming penetrance of 70%.
- If neither parent has a disease-causing mutation detectable in DNA, it is presumed that the proband has a *de novo* gene mutation and the risk to the sibs of the proband depends on the spontaneous mutation rate of ADNFLE and the probability of germline mosaicism.

Offspring of a proband. The risk to each offspring of a proband of inheriting the mutant allele is 50%. The chance that the offspring will manifest ADNFLE is (50%)(70%)=35%, assuming penetrance of 70%.

Other family members. The risk to other family members depends upon the genetic status of the proband's parents and the presence of other affected first- or second-degree relatives. If a parent is found to be affected or to have a disease-causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

Other genetic counseling issues. Individuals may not be aware of the significance of their attacks [Scheffer et al 1995, Thomas et al 1998]. In some families, individuals may be reluctant to reveal their symptoms [Scheffer et al 1995, Thomas et al 1998].

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and genetic counseling is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically been extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis for ADNFLE are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as ADNFLE that do not usually affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussions of these issues is appropriate.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Nocturnal Frontal Lobe Epilepsy, Autosomal Dominant

Gene Symbol	Chromosomal Locus	Protein Name
CHRNA4	20q13.2-q13.3	Neuronal acetylcholine receptor protein, alpha-4 chain
CHRNB2	1q21	Neuronal acetylcholine receptor protein, beta-2 chain

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Nocturnal Frontal Lobe Epilepsy, Autosomal Dominant

118504	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 4; CHRNA4
118507	CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 2; CHRNB2
600513	EPILEPSY, NOCTURNAL FRONTAL LOBE, TYPE 1
605375	EPILEPSY, NOCTURNAL FRONTAL LOBE, TYPE 3

Table C. Genomic Databases for Nocturnal Frontal Lobe Epilepsy, Autosomal Dominant

Gene Symbol	Entrez Gene	HGMD
CHRNA4	1137 (MIM No. 118504)	CHRNA4
CHRNB2	1141 (MIM No. 118507)	CHRNB2

For a description of the genomic databases listed, click here.

Molecular Genetic Pathogenesis

The normal neuronal nicotinic acetylcholine receptor. The neuronal acetylcholine receptor is a heterologous pentamer comprising various combinations of alpha and beta subunits. The most common configuration consists of α4ß2 subunits, encoded by the *CHRNA4* and *CHRNB2* genes. The receptor is widely distributed in the brain, including the frontal lobes [Wevers et al 1994].

CHRNA4 and *CHRNB2* gene mutations associated with ADNFLE occur in highly conserved amino acids and alter the function of the resulting receptors. The second transmembrane domain forms the ion channel pore and is the site of all the mutations implicated in ADNFLE. Functional studies of different mutations provide conflicting results [Steinlein et al 1995, Kurayatov et al 1997, Steinlein et al 1997, Bertrand et al 1998, Bertrand 1999, De Fusco et al 2000, Phillips et al 2001]; thus, the mechanism whereby the mutations cause ADNFLE is poorly understood. It is thought that the receptor acts as 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 [Wevers et al 1994, Kurayatov et al 1997, Bertrand 1999, Buisson et al 1999, Picard et al 1999].

CHRNA4

Normal allelic variants: The *CHRNA4* gene has six exons distributed over approximately 17kb of genomic DNA and lies between the polymorphic markers D20S20 and D20S24 [Steinlein et al 1996]. The main part of the coding region is distributed in exon 5 [Steinlein et al 1996]. Polymorphic allelic variants of the *CHRN* receptor genes have been described [Steinlein 1995, Weiland & Steinlein 1996, Phillips & Mulley 1997].

Pathologic allelic variants:

Table 2. Mutated Neuronal Nicotinic Acetylcholine Genes in ADNFLE

CHRNA4	S248F/S252F [1]	Three families [Steinlein et al 1995, Saenz et al 1999, Steinlein et al 2000]
	C755T/S252L	Three families [Hirose et al 1999, Phillips et al 2000, Cho et al 2003]
	776ins3	One family [Steinlein et al 1997]

1. S248F and S252F represent the same mutation, but refer to Torpedo torpedo amino acid numbering and human amino acid number respectively.

Normal gene product: Each nicotinic acetylcholine receptor 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 alpha subunits are characterized by the presence of a pair of cysteine residues (C133 and C147) that are presumed to function as part of the Ach binding site when the α4 subunits are complexed as a heterologous pentamer with the ß subunits [Figl et al 1998].

Abnormal gene product: Various mutations resulting in changes in the highly conserved region of the conducting pore or transmembrane domain are described [Figl et al 1998, Steinlein 1999].

CHRNB2

Normal allelic variants: The gene *CHRNB2* is similar to *CHRNA4*, but the beta subunits encoded by the genes are defined by the lack of paired cysteine residues [Elliott et al 1996]. Polymorphic allelic variants of the *CHRN* receptor genes have been described in the literature [Steinlein 1995, Weiland & Steinlein 1996, Phillips & Mulley 1997].

Pathologic allelic variants:

Table 3. Mutated Neuronal Nicotinic Acetylcholine Genes in ADNFLE

CHRNB2	G1025C/V287L	One family [De Fusco et al 2000]
	G1025A/V287M	Two families [Diaz-Otero et al 2001, Phillips et al 2001]

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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References

Medical Genetics Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

American Sleep Disorders Association. International classification of sleep disorders, revised: diagnostic and coding manual. American Sleep Disorders Association, Rochester, MN. 1997

Bertrand D. Neuronal nicotinic acetylcholine receptors: their properties and alterations in autosomal dominant nocturnal frontal lobe epilepsy. Rev Neurol (Paris). 1999;155:457–62. [PubMed: 10472659]

Bertrand S, Weiland S, Berkovic SF, Steinlein OK, Bertrand D. Properties of neuronal nicotinic acetylcholine receptor mutants from humans suffering from autosomal dominant nocturnal frontal lobe epilepsy. Br J Pharmacol. 1998;125:751–60. [PubMed: 9831911]

Bonati MT, Combi R, Asselta R, Duga S, Malcovati M, Oldani A, Zucconi M, Ferini-Strambi L, Dalpra L, Tenchini ML. Exclusion of linkage of nine neuronal nicotinic acetylcholine receptor subunit genes expressed in brain in autosomal dominant nocturnal frontal lobe epilepsy in four unrelated families. J Neurol. 2002;249:967–74. [PubMed: 12195439]

Buisson et, al. Neuronal nicotinic acetylcholine receptor and epilepsy. In: Berkovic SF et al (eds) Genetics of Focal Epilepsies. John Libbey and Co. 1999

Buruma O, et al. Paroxysmal choreoathetosis. In: Vinken P, et al (ed) Handbook of Clinical Neurology, Extrapyramidal Disorders, v 5. Elsevier Science. 1986

Byrne E, White O, Cook M. Familial dystonic choreoathetosis with myokymia; a sleep responsive disorder. J Neurol Neurosurg Psychiatry. 1991;54:1090–2. [PubMed: 1783923]

Cho YW, Motamedi GK, Laufenberg I, Sohn SI, Lim JG, Lee H, Yi SD, Lee JH, Kim DK, Reba R, Gaillard WD, Theodore WH, Lesser RP, Steinlein OK. A Korean kindred with autosomal dominant nocturnal frontal lobe epilepsy and mental retardation. Arch Neurol. 2003;60:1625–32. [PubMed: 14623738]

De Fusco M, Becchetti A, Patrignani A, Annesi G, Gambardella A, Quattrone A, Ballabio A, Wanke E, Casari G. The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. Nat Genet. 2000;26:275–6. [PubMed: 11062464]

Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. Ann Neurol. 1995;38:571–9. [PubMed: 7574453]

Diaz-Otero F, et al. A Spanish family with autosomal dominant nocturnal frontal lobe epilepsy and a mutation in the CHRNB2 gene. Epilepsia 42(S7) AES Proceedings 2001, Abstract 1.056, p 21. 2001

Elliott KJ, Ellis SB, Berckhan KJ, Urrutia A, Chavez-Noriega LE, Johnson EC, Velicelebi G, Harpold MM. Comparative structure of human neuronal alpha 2-alpha 7 and beta 2-beta 4 nicotinic acetylcholine receptor subunits and functional expression of the alpha 2, alpha 3, alpha 4, alpha 7, beta 2, and beta 4 subunits. J Mol Neurosci. 1996;7:217–28. [PubMed: 8906617]

Figl A, Viseshakul N, Shafaee N, Forsayeth J, Cohen BN. Two mutations linked to nocturnal frontal lobe epilepsy cause use-dependent potentiation of the nicotinic ACh response. J Physiol 513 (Pt. 1998;3): 655–70. [PubMed: 9824708]

Gambardella A, Annesi G, De Fusco M, Patrignani A, Aguglia U, Annesi F, Pasqua AA, Spadafora P, Oliveri RL, Valentino P, Zappia M, Ballabio A, Casari G, Quattrone A. A new locus for autosomal dominant nocturnal frontal lobe epilepsy maps to chromosome 1. Neurology. 2000;55:1467–71. [PubMed: 11094099]

Hayman M, Scheffer IE, Chinvarun Y, Berlangieri SU, Berkovic SF. Autosomal dominant nocturnal frontal lobe epilepsy: demonstration of focal frontal onset and intrafamilial variation. Neurology. 1997;49:969–75. [PubMed: 9339675]

Hirose S, Iwata H, Akiyoshi H, Kobayashi K, Ito M, Wada K, Kaneko S, Mitsudome A. A novel mutation of CHRNA4 responsible for autosomal dominant nocturnal frontal lobe epilepsy. Neurology. 1999;53:1749–53. [PubMed: 10563623]

Ito M, Kobayashi K, Fujii T, Okuno T, Hirose S, Iwata H, Mitsudome A, Kaneko S. Electroclinical picture of autosomal dominant nocturnal frontal lobe epilepsy in a Japanese family. Epilepsia. 2000;41:52–8. [PubMed: 10643924]

Khatami R, Neumann M, Schulz H, Kolmel HW. A family with autosomal dominant nocturnal frontal lobe epilepsy and mental retardation. J Neurol. 1998;245:809–10. [PubMed: 9840354]

Kuryatov A, Gerzanich V, Nelson M, Olale F, Lindstrom J. Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca2+ permeability, conductance, and gating of human alpha4beta2 nicotinic acetylcholine receptors. J Neurosci. 1997;17:9035–47. [PubMed: 9364050]

Lance JW. Familial paroxysmal dystonic choreoathetosis and its differentiation from related syndromes. Ann Neurol. 1977;2:285–93. [PubMed: 617268]

Lugaresi E, Cirignotta F. Hypnogenic paroxysmal dystonia: epileptic seizure or a new syndrome? Sleep. 1981;4:129–38. [PubMed: 7256073]

Magnusson A, Stordal E, Brodtkorb E, Steinlein O. Schizophrenia, psychotic illness and other psychiatric symptoms in families with autosomal dominant nocturnal frontal lobe epilepsy caused by different mutations. Psychiatr Genet. 2003;13:91–5. [PubMed: 12782965]

Mochi M, Provini F, Plazzi G, Corsini R, Farnedi F, Tinuper P, Valentino ML, Lugaresi E, Montagna P. Genetic heterogeneity in autosomal dominant nocturnal frontal lobe epilepsy. Ital J Neurol Sci. 1997;18:183. [PubMed: 9241568]

Montagna P. Nocturnal paroxysmal dystonia and nocturnal wandering. Neurology. 1992;42:61–7. [PubMed: 1630641]

Montagna P, Sforza E, Tinuper P, Cirignotta F, Lugaresi E. Paroxysmal arousals during sleep. Neurology. 1990;40:1063–6. [PubMed: 2356007]

Mount L, et al. Familial paroxysmal choreoathetosis. Arch Neurol. 1940;44:841–7.

Nakken KO, Magnusson A, Steinlein OK. Autosomal dominant nocturnal frontal lobe epilepsy: an electroclinical study of a Norwegian family with ten affected members. Epilepsia. 1999;40:88–92. [PubMed: 9924907]

Oldani A, Zucconi M, Asselta R, Modugno M, Bonati MT, Dalpra L, Malcovati M, Tenchini ML, Smirne S, Ferini-Strambi L. Autosomal dominant nocturnal frontal lobe epilepsy. A video-polysomnographic and genetic appraisal of 40 patients and delineation of the epileptic syndrome. Brain 121 (Pt. 1998;2):205–23. [PubMed: 9549500]

Oldani A, Zucconi M, Ferini-Strambi L, Bizzozero D, Smirne S. Autosomal dominant nocturnal frontal lobe epilepsy: electroclinical picture. Epilepsia. 1996;37:964–76. [PubMed: 8822695]

Phillips HA, Favre I, Kirkpatrick M, Zuberi SM, Goudie D, Heron SE, Scheffer IE, Sutherland GR, Berkovic SF, Bertrand D, Mulley JC. CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. Am J Hum Genet. 2001;68:225–31. [PubMed: 11104662]

Phillips HA, Marini C, Scheffer IE, Sutherland GR, Mulley JC, Berkovic SF. A de novo mutation in sporadic nocturnal frontal lobe epilepsy. Ann Neurol. 2000;48:264–7. [PubMed: 10939581]

Phillips HA, Mulley JC. SSCP variants within the alpha 4 subunit of the neuronal nicotinic acetylcholine receptor gene. Clin Genet. 1997;51:135–6. [PubMed: 9112007]

Phillips HA, Scheffer IE, Crossland KM, Bhatia KP, Fish DR, Marsden CD, Howell SJ, Stephenson JB, Tolmie J, Plazzi G, Eeg-Olofsson O, Singh R, Lopes-Cendes I, Andermann E, Andermann F, Berkovic SF, Mulley JC. Autosomal dominant nocturnal frontal-lobe epilepsy: genetic heterogeneity and evidence for a second locus at 15q24. Am J Hum Genet. 1998;63:1108–16. [PubMed: 9758605]

Picard F, Baulac S, Kahane P, Hirsch E, Sebastianelli R, Thomas P, Vigevano F, Genton P, Guerrini R, Gericke CA, An I, Rudolf G, Herman A, Brice A, Marescaux C, LeGuern E. Dominant partial epilepsies. A clinical, electrophysiological and genetic study of 19 European families. Brain 123 (Pt. 2000;6):1247–62. [PubMed: 10825362]

Picard F, Bertrand S, Steinlein OK, Bertrand D. Mutated nicotinic receptors responsible for autosomal dominant nocturnal frontal lobe epilepsy are more sensitive to carbamazepine. Epilepsia. 1999;40:1198–209. [PubMed: 10487182]

Provini F, Plazzi G, Tinuper P, Vandi S, Lugaresi E, Montagna P. Nocturnal frontal lobe epilepsy. A clinical and polygraphic overview of 100 consecutive cases. Brain 122 (Pt. 1999;6):1017–31. [PubMed: 10356056]

Rozycka A, Skorupska E, Kostyrko A, Trzeciak WH. Evidence for S284L mutation of the CHRNA4 in a white family with autosomal dominant nocturnal frontal lobe epilepsy. Epilepsia. 2003;44:1113–7. [PubMed: 12887446]

Saenz A, Galan J, Caloustian C, Lorenzo F, Marquez C, Rodriguez N, Jimenez MD, Poza JJ, Cobo AM, Grid D, Prud homme JF, Lopez de Munain A. Autosomal dominant nocturnal frontal lobe epilepsy in a Spanish family with a ser252 mutation in the CHRNA4 gene. Arch Neurol. 1999;56:1004–9. [PubMed: 10448807]

Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann F, Andermann E, Desbiens R, Cendes F, Manson JI, et al. Autosomal dominant frontal epilepsy misdiagnosed as sleep disorder. Lancet. 1994;343:515–7. [PubMed: 7906762]

Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, Andermann F, Desbiens R, Keene D, Cendes F, et al. Autosomal dominant nocturnal frontal lobe epilepsy. A distinctive clinical disorder. Brain 118 (Pt. 1995;1):61–73. [PubMed: 7895015]

Schenck CH, Mahowald MW. Parasomnias. Managing bizarre sleep-related behavior disorders. Postgrad Med. 2000;107:145–56. [PubMed: 10728141]

Sforza E, Montagna P, Rinaldi R, Tinuper P, Cerullo A, Cirignotta F, Lugaresi E. Paroxysmal periodic motor attacks during sleep: clinical and polygraphic features. Electroencephalogr Clin Neurophysiol. 1993;86:161–6. [PubMed: 7680991]

Steinlein O, Weiland S, Stoodt J, Propping P. Exon-intron structure of the human neuronal nicotinic acetylcholine receptor alpha 4 subunit (CHRNA4). Genomics. 1996;32:289–94. [PubMed: 8833159]

Steinlein OK. Detection of a CfoI polymorphism within exon 5 of the human neuronal nicotinic acetylcholine receptor alpha 4 subunit gene (CHRNA4). Hum Genet. 1995;96:130. [PubMed: 7607646]

Steinlein OK. Molecular biology in autosomal dominant nocturnal frontal lobe epilepsy. In: Berkovic SF, et al (eds) Genetics of Focal Epilepsies. John Libbey and Co, pp 187-202. 1999

Steinlein OK, Magnusson A, Stoodt J, Bertrand S, Weiland S, Berkovic SF, Nakken KO, Propping P, Bertrand D. An insertion mutation of the CHRNA4 gene in a family with autosomal dominant nocturnal frontal lobe epilepsy. Hum Mol Genet. 1997;6:943–7. [PubMed: 9175743]

Steinlein OK, Mulley JC, Propping P, Wallace RH, Phillips HA, Sutherland GR, Scheffer IE, Berkovic SF. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 1995;11:201–3. [PubMed: 7550350]

Steinlein OK, Stoodt J, Mulley J, Berkovic S, Scheffer IE, Brodtkorb E. Independent occurrence of the CHRNA4 Ser248Phe mutation in a Norwegian family with nocturnal frontal lobe epilepsy. Epilepsia. 2000;41:529–35. [PubMed: 10802757]

Tenchini ML, Duga S, Bonati MT, Asselta R, Oldani A, Zucconi M, Malcovati M, Dalpra L, Ferini-Strambi L. SER252PHE and 776INS3 mutations in the CHRNA4 gene are rare in the Italian ADNFLE population. Sleep. 1999;22:637–9. [PubMed: 10450598]

Thomas P, Picard F, Hirsch E, Chatel M, Marescaux C. Autosomal dominant nocturnal frontal lobe epilepsy. Rev Neurol (Paris). 1998;154:228–35. [PubMed: 9773047]

Vigevano F, Fusco L. Hypnic tonic postural seizures in healthy children provide evidence for a partial epileptic syndrome of frontal lobe origin. Epilepsia. 1993;34:110–9. [PubMed: 8422842]

Weiland S, Steinlein O. Dinucleotide polymorphism in the first intron of the human neuronal nicotinic acetylcholine receptor alpha 4 subunit gene (CHRNA4). Clin Genet. 1996;50:433–4. [PubMed: 9007339]

Wevers A, Jeske A, Lobron C, Birtsch C, Heinemann S, Maelicke A, Schroder R, Schroder H. Cellular distribution of nicotinic acetylcholine receptor subunit mRNAs in the human cerebral cortex as revealed by non-isotopic in situ hybridization. Brain Res Mol Brain Res. 1994;25:122–8. [PubMed: 7984036]

Chapter Notes

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