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EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias

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Objectives: These EFNS guidelines on the molecular diagnosis of channelopathies, including epilepsy and migraine, as well as stroke, and dementia are designed to summarize the possibilities and limitations of molecular genetic techniques and to provide diagnostic criteria for deciding when a molecular diagnostic work-up is indicated.

Search strategy: To collect data about planning, conditions, and performance of molecular diagnosis of these disorders, a literature search in various electronic databases was carried out and original papers, meta-analyses, review papers, and guideline recommendations were reviewed.

Results: The best level of evidence for genetic testing recommendation (B) can be found for a small number of syndromes, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, severe myoclonic epilepsy of infancy, familial recurrent hemorrhages, familial Alzheimer's disease, and frontotemporal lobar degeneration. Good practice points can be formulated for a number of other disorders.

Conclusion: These guidelines are provisional, and the future availability of molecular genetic epidemiological data about the neurogenetic disorders under discussion in our article will allow improved recommendation with an increased level of evidence.

Introduction

Since the publication of the first EFNS guidelines on the molecular diagnosis of inherited neurological diseases in 2001 [1,2], rapid progress has been made in this field, necessitating the creation of an updated version of these guidelines, which follows the EFNS Scientific Committee recommendations for guideline papers [3].

Objectives: These EFNS guidelines on the molecular diagnosis of channelopathies, including epilepsy and migraine, as well as stroke, and dementia are designed to summarize the possibilities and limitations of molecular genetic techniques and to provide diagnostic criteria for deciding when a molecular diagnostic work-up is indicated in adults.

Search strategy: To collect data about planning, conditions, and performance of molecular diagnosis of

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these disorders, a literature search in various electronic databases, such as Cochrane library, MEDLINE, OMIM, GENETEST, or Embase was carried out and original papers, meta-analyses, review papers, and guideline recommendations were reviewed.

Method for reaching consensus: Consensus about the recommendations was reached by a step-wise approach. First, task force members met at the EFNS congresses in 2007 and 2008 to discuss the preparations of the guidelines. In a second step, experts in genetics of the disorders mentioned previously wrote a guideline proposal. In a third step, these recommendations were distributed and discussed in detail among all task force members until a final consensus had been reached.

Results and recommendations: Recommendations follow the criteria established by the EFNS [3], with some modifications to account for the specific nature of genetic tests. As genetic testing is by definition the gold standard to diagnose a genetically defined disease, its diagnostic accuracy cannot be tested against another diagnostic method. Therefore, the level of recommendations was based on the quality of available studies [3], and the proportion of cases of a clinically defined group of patients that are explained by a specific molecular diagnostic test was estimated. As nearly all of these studies have a retrospective design and look for a specific mutation in a previously ascertained and clinically diagnosed cohort of patients, the highest achievable recommendation level was B [3]. If only small case-series studying genotype–phenotype correlations were available, the level of recommendation was C. If only case reports could be found, but experts still felt that they could give a recommendation, the level of recommendation was assessed as 'good practice point.'

Channelopathies

Ion channels are trans-membrane proteins, which allow fluxes between the intra- and extracellular spaces with specific conductance for different ions, including sodium, calcium, chloride, and other. Voltage-gated activation modulates membrane excitability, allowing intercellular communication and impulse propagation. Ion channel gene mutations have been found in neurological disorders, which have in common episodic or paroxysmal clinical manifestations. Muscle channelopathies include periodic paralysis, non-dystrophic myotonia, Andersen–Tawil syndrome, and congenital myasthenia. Disorders affecting the central nervous system comprise episodic ataxia, migraine, and epilepsy. Molecular diagnosis is now available for many neurological channelopathies (Table 1).

Muscular channelopathies

Hypokalemic periodic paralysis is an autosomal dominant hereditary disease [4] characterized by episodic muscle paralysis concomitant with a decrease in blood potassium levels and facilitated by muscle exercise or sugar ingestion. Between attacks, muscle examination is normal. The disease may be caused by specific mutations either in the calcium channel α1S-subunit (*CACNA1S*) gene, localized on chromosome 1, or in the sodium channel α1-subunit (*SCN4A*) on chromosome

Table 1 Neurological channelopathies

Disease	Gene	Mode of inheritance	Gene locus	Mutated protein	OMIM
Hypokalemic periodic paralysis (HOKPP)	*CACNA1S*	AD	1q32	Calcium channel α1S subunit type 1	170400
	SCN4A	AD	17q23	Sodium channel α-subunit type 4	170400
Hyperkalemic periodic paralysis (HYPP)	*SCN4A*	AD	17q23	Sodium channel α-subunit type 4	170500
Paramyotonia congenita (PMC)					168300
Sodium channel myotonia or potassium-aggravated myotonia					608390
Myotonia congenita	*CLCN1*	AD (Thomsen)	7q35	Chloride channel type 1	160800
		AR (Becker)	7q35		255700
Andersen–Tawil syndrome (ATS)	*KCNJ2*	AD	17q23	Potassium channel subfamily J member 2	170390
Congenital myasthenic syndrome (CMS)	*SCN4A*	AD	17q23	Sodium channel α-subunit type 4	603967
Benign neonatal epilepsy (BNE1, 2)	*KCNQ2*	AD	20q13	Potassium channel subfamily Q member 2	121200
	KCNQ3	AD	8q24	Potassium channel subfamily Q member 3	121201
Benign familial neonatal–infantile seizures	*SCN2A*	AD	2q24	Sodium channel α-subunit type 2	607745
Generalized epilepsy with febrile seizure-plus (GEFS+)	*SCN1B*	AD	19q13	Sodium channel β-subunit type 1	604233
	SCN1A	AD	2q24	Sodium channel α-subunit type 1	
Severe myoclonic epilepsy of infancy (SMEI)	*SCN1A*	AD	2q24	Sodium channel α-subunit type 1	607208
Juvenile myoclonic epilepsy	*CLCN2*	AR	3q26	Chloride channel type 2	606904
Childhood absence epilepsy	*CLCN2*	AR	3q26	Chloride channel type 2	607682

17. Mutations in *CACNA1S*, found in 70–90% of patients from different ethnic backgrounds, are the most frequent. Patients with *SCN4A* mutations tend to have muscle aches and drug-induced symptom aggravation [5]. *In vitro* expression of mutated channels suggests a loss-of-function mechanism and an increased 'leakiness' of the channels [6]. Mechanisms underlying blood potassium level changes are still not well understood. Electromyography following sensitization by a long exercise test allows diagnosis of periodic paralysis even between attacks and may predict channel type mutation [7]. Treatment relies on the avoidance of provocative factors and the use of chloride potassium salts and acetazolamide.

Hyperkalemic periodic paralysis, paramyotonia congenita, and sodium channel myotonia have in common to be caused by distinct mutations of the sodium channel gene *SCN4A* on chromosome 17 [8–10]. Overlapping syndromes with different degrees of paralysis and myotonia occur depending on the mutation. Hyperkalemic periodic paralysis is characterized by episodic attacks of muscle weakness concomitant with increased blood potassium levels. Provocation factors include muscle exercise, cold, alcohol, potassium-rich food, stress, or steroids. Paramyotonia congenita is characterized by prolonged muscle contraction aggravated by exercise (paradoxical myotonia) and cold. Distinct patterns of spontaneous activity, possibly related to the mutation type, may be recorded on needle electromyography [11]. All these disorders are transmitted with an autosomal dominant mode of inheritance and are caused by mutations in *SCN4A* distinct from the ones implicated in hypokalemic periodic paralysis. Although there may be variations between and within families, there is a good genotype–phenotype correlation. *In vitro* expression of mutated channels has revealed that they may activate early or inactivate late or incompletely resulting in increased excitability of the cell membrane. A slight increase in excitability will result in an increased number of action potentials and thus myotonia. Treatment is based on the avoidance of provoking factors, mild exercise at onset of an attack, or intake of carbohydrates. Acetazolamide may prevent the attacks of muscle weakness. Blockers of the open states of the sodium channel (mexiletine, carbamazepine, and diphenylhydantoin) can alleviate myotonia [12].

Neuronal channelopathies

Neuronal channelopathies comprise a variety of disorders including episodic ataxias, migraine, and some forms of epilepsy [13]. Ataxias are discussed in another study of this series and migraine later. Rare inherited forms of epilepsy are increasingly recognized as channelopathies. Benign infantile neonatal epilepsy (*EBN1*, *EBN2*) is an autosomal dominant condition, in which newborns develop tonic-clonic seizures within the first days of life. Neurological development is normal, and the seizures are easily controlled by antiepileptic medication. The disease is caused by loss-of-function mutations in either the potassium channel gene *KCNQ2* or *KCNQ3* (Table 1). In autosomal dominant benign familial neonatal–infantile seizures, mutations have been found in the gene encoding the neuronal sodium channel α-subunit (*SCN2A*) on chromosome 2. Generalized epilepsy with febrile seizures-plus (GEFS+) is an autosomal dominant condition with different types of seizures (febrile seizures, generalized seizures, and partial seizures). Mutations were found in the genes encoding the β1-subunit of the sodium channel (*SCN1B*), the α1-subunit of the neuronal sodium channel (*SCN1A*), and in the *GABRG2* gene. In severe myoclonic epilepsy of infancy (SMEI), seizures are refractory to medication, and patients develop neurological deterioration because of de novo mutations in the gene encoding the α1-subunit of the neuronal sodium channel *SCN1A* on chromosome 2. Juvenile myoclonic epilepsy has an onset in adolescence with a combination of myoclonic, generalized, and absence seizures. Mutations were found in the gene encoding the chloride channel *CLCN2* on chromosome 3. Mutations in *CLCN2* have also been linked to childhood absence epilepsy, a condition of good prognosis characterized by multiple absences beginning in mid-childhood with generalized 3Hz spike-and-wave complexes.

Recommendations

There is good evidence to suggest that a thorough clinical and electrophysiological investigation may lead to the choice of the gene to be tested in patients with periodic paralysis (level B). In myotonic disorders, it is recommended to first search for myotonic dystrophy and use clinical and electrophysiological phenotype characterization to guide for molecular genetic testing (level B).

Molecular investigations are possible and may help in some cases to diagnose the condition but cannot be considered as a routine procedure with regard to the large number of different mutations in different genes. Furthermore, diagnosis can be made more easily by clinical and physiological investigations (good practice point). One exception of note is the diagnosis of SMEI, in which mutations are found in *SCN1A* in 80% of the patients (level B).

Cerebrovascular diseases

CADASIL

The main clinical features of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukencephalopathy (CADASIL) include migraine with aura in the third decade of life, recurrent ischaemic stroke or transitory ischaemic attacks 10 years later, followed by dementia 20 years after onset. The disorder results from mutations in the gene coding for Notch3 located on chromosome 19q12 (Table 2). Mutations are localized in coding regions for epidermal growth factor (EGF)-like repeat domains. Most of the mutations (70%) are clustered within exons 3 and 4. Direct sequencing of these two exons is suggested as a first step if clinical suspicion is high. Multiple small subcortical infarcts with leukoaraiosis are typically found in the frontal poles [14]. The diagnosis may also be supported by skin biopsy showing typical osmiophilic granula.

Amyloid angiopathies

Cerebral amyloid angiopathy (CAA), Dutch type is caused by a point mutation within the amyloid precursor protein (*APP*) gene (guanine-to-cytosine at nucleotide 1852), resulting in a substitution of glutamine for glutamic acid at position 693 (Table 2). Several other *APP* mutations in Alzheimer disease (AD) are associated with a strong microvascular amyloid involvement [15]. The Icelandic type CAA results from a point mutation within the cystatin C gene with a change of leucine in position 68 to glutamine. CAA should be considered in patients with early onset of recurrent cerebral hemorrhages in association with prominent white matter changes.

Cavernous malformations

Cerebral cavernous malformations (CCM) are vascular malformations causing hemorrhagic or ischaemic strokes. Approximately half of the cases are inherited as an autosomal dominant trait with incomplete penetrance. Most of the CCM cases result from mutations in the *KRIT1* gene (Table 2), localized on chromosome 7q21–22 (CCM1) [16]. Mutations seem to be distributed over the entire coding sequence. Mutational analysis can be considered in patients with multiple cavernomas or a family history of cerebral hemorrhages. However, at-risk individuals may also be identified by MR-scanning. Two additional loci CCM2 (OMIM 603 284) and CCM3 (OMIM 603 285) have been localized to chromosomes 7p13–15 and 3q25.2–27, respectively.

Fabry's disease

Fabry's disease is an X-linked systematic disorder resulting from deficiency of the lysosomal enzyme alpha-galactosidase A. Early clinical features such as angiokeratoma, hypohidrosis typically occur in child-

Table 2 Main genetic causes of stroke and migraine

Disease	Gene product	Mutation	Position	Mode of transmission	OMIM
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Notch3	Point mutations	19q12	AD	125 310
Cerebral amyloid angiopathy (CAA, Dutch Type)	Amyloid Precursor Protein	Point mutations	21q21	AD	104 760
Cerebral amyloid angiopathy (CAA, Icelandic Type)	Cystatin C	L68Q mutation	20p11.2	AD	105 150
Cerebral cavernous malformations	CCM1	Point mutations deletions	7q21–22	AD (incomplete penetrance)	116 860
Cerebral cavernous malformations	CCM2	Point mutations deletions	7p13–15	AD (incomplete penetrance)	603 284
Cerebral cavernous malformations	CCM3	Point mutations deletions	3q25.2 ± 27	AD (incomplete penetrance)	603 285
Familial hemiplegic migraine (FHM)	CACNA1A	Point mutations,	19p13	AD	141 500
Elevated level of serum homocysteine	Methylenetetrahydrofolate reductase enzyme (MTHFR)	Point mutations	1p36.3	AR	607 093
Elevated level of serum homocysteine	Cystatione β-synthetase enzyme (CBS)	Missense, nonsense, splicing, deletion, insertion mutations	21q22.3	AR	236 200

hood. Kidney, heart, and brain involvement may develop in mid-adulthood. Cerebrovascular involvement includes both large-vessel and small-vessel disease resulting in ischaemic lesions or vascular demyelization of the white matter. Diagnosis may be confirmed by measuring alpha-galactosidase A activity or by screening for mutations. Because of X-linked inheritance, in women, mutation screening may be required.

Homocystinuria

Homocystinuria results from a group of mostly autosomal recessive enzyme deficiencies, which are associated with a highly or mildly elevated level of serum homocysteine (>15 μM). The majority of the patients with a highly elevated serum homocysteine level have a thrombembolic stroke or stroke-like episodes, if they are not treated. Screening for mutations in the cystatione β-synthetase and methylenetetrahydrofolate reductase gene is available. Correlation between mutations, homocysteine serum level, and clinical phenotype is influenced by several biochemical conditions such as folic acid and B vitamin daily uptake.

The cystatione β-synthetase enzyme deficiency has been associated with several missense, nonsense, splicing, deletion, or insertion mutations. A permanent or temporary (thermo-sensitive) decrease in the activity of the methylenetetrahydrofolate reductase enzyme can also result from C677T or A1298C mutations. The above relatively frequent mutations are associated with mostly autosomal recessive enzyme deficiencies.

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome type IV is an autosomal dominant disorder caused by mutations in *COL3A1* gene. The main clinical features are easy bruising, hyperextensibility of joints, thin skin with visible veins, and rupture of arteries, uterus, or intestines. Arterial dissection in large- and medium-sized arteries can account for ischaemic stroke.

Recommendations

Direct sequencing of exons 3 and 4 in the Notch3 gene is suggested as a first step if clinical suspicion for CADASIL is high (level B). CCA should be considered in patients with early-onset, recurrent cerebral hemorrhages in association with prominent white matter lesions without classic clinical risk factors. In such cases, the *KRIT1* gene should be screened for causative mutations (level B). Genetic tests for Fabry's disease are suggested in the case of neuropathic pain, hypohydrosis, acroparesthesia, corneal opacities, cataract, renal failure, cardiac failure, ischaemic stroke, or TIAs (level B). Mutation screening in Ehlers-Danlos syndrome can be performed in case of clinical implications (easy bruising, hyperextensibility of joints, thin skin with visible veins, rupture of arteries, uterus or intestines, and arterial dissection) (good practice point). In the event of a stroke attack with elevated level of serum homocysteine (>15 μM), screening for mutations in cystatione beta-synthetase and methylenetetrahydrofolate reductase is suggested (level B).

Migraine

Familial hemiplegic migraine

FHM is inherited in an autosomal dominant way. Most of the cases are linked to a locus on chromosome 19p13, and in some instances, point mutations have been described in the alpha1 subunit of the calcium channel gene (*CACNA1A*). Point mutations in the same gene cause episodic ataxia type 2 (EA2), and the expansion of a CAG-repeat is responsible for spinocerebellar ataxia type 6 (SCA6). Clinical presentation and genetic findings overlap between all three conditions. A minority of affected families is linked to a second locus on chromosome 1q23 (*ATP1A2*), and a mutation in the neuronal voltage-gated sodium channel gene (*SCN1A*) has recently been described (Table 2).

Recommendations

The diagnosis of familial hemiplegic migraine can be confirmed with sequencing the hot spots of the most often affected gene (*CACNA1A*) (good practice point).

Inherited dementias

The majority of degenerative dementias occur with an autosomal dominant inheritance pattern and similar phenotypes to sporadic disease. The proportion of familial occurrence varies between 2% and 50%, depending on the dementia subtype. In dementing disorders, it is particularly important to ensure adequate genetic counseling and obtain consent from the patient and/or family caregiver prior to any attempt of molecular genetic diagnosis [17]. It also needs to be pointed out that a postmortem diagnosis of the cause of a familial degenerative dementia can provide critically important information for future counseling of the family and should be discussed. In most instances, molecular genetic diagnosis will only be feasible in patients with a clear family history that is indicative of a monogenic form of the disease or in sporadic occurrences with an unusually early age of onset. Because of

reduced penetrance, however, some known dominant mutations can also cause seemingly sporadic late-onset disease in some populations even in a surprisingly high proportion of cases.

Alzheimer's disease

Alzheimer's disease is the most common type of primary degenerative dementia. Clinical features include a slow, progressive amnesic syndrome and variable combinations of other cortical cognitive deficits but also include behavioral changes and affective symptoms. Mutations in three genes have been found to cause an autosomal dominant form of the disease (sometimes referred to as AD type 1, 3, and 4) [18], and together these account for $<5\%$ of all cases (Table 3) (http://www.molgen.ua.ac.be/ADMutations). Among them, AD3, which is caused by mutations in the presenilin 1 gene (*PSEN1*) on chromosome 14, is the most common. In contrast, AD1, due to mutations in the gene for the amyloid precursor protein (*APP*, OMIM 104760, chromosome 21), and AD4 with mutations in the presenilin 2 gene (*PSEN2*, OMIM 600759, chromosome 1) are rare [19]. *APP* encodes a transmembrane protein that gives rise, after proteolytic cleavage, to Aß-fragments that pathologically aggregate in amyloid plaques thought to be at the centre of the pathogenic cascade in AD [20]. Point mutations in coding regions as well as whole gene duplications and promoter mutations increasing transcriptional activity have been shown to lead to AD [15,21]. The presenilins are part of the proteolytic complex known as the γ-secretase that cleaves APP and releases the Aß-fragment. *PSEN1* mutations are probably pathogenic because of the fact that they increase the relative ratio of the more amyloidogenic $A\beta_{1-42}$ fragment to $A\beta_{1-40}$. An earlier onset age between 30 and 60 years is common in monogenic forms, although *PSEN1* mutations have also been detected in patients with onset at ages over 60–70 years. When accompanied by a positive family history, molecular genetic testing should be considered. Several specialized laboratories across Europe provide such testing. Here, the probability of identifying a mutation in one of the three AD genes is approximately 10%, in case the patient has a clear autosomal dominant inheritance, the chance increases to 20%. Mutation screening can also be offered to apparently sporadic patients with a diagnosis age below 70, with a chance of approximately 5% to find a mutation. In addition to the mutations mentioned previously that can cause AD with high penetrance, a common variant of the apolipoprotein E gene (*APOE*) known as the ϵ4-allele has been clearly established as a risk factor for early and late-onset AD (AD2). As the *APOE* ϵ4-allele is neither necessary nor sufficient to cause AD, there is a wide consensus that at present there is no clear benefit in *APOE* genotyping to assist with diagnosis [22] or pre-symptomatic risk assessment. One exception involves *APOE* genotyping in individuals carrying a causal mutation in *PSEN1*, *APP,* or *PSEN2,* because the *APOE* ϵ4-allele can lower the age of onset by approximately 5 years in mutation carriers. A growing number of other loci (AD5–15 in the 'OMIM'-catalogue) and genes have been suggested. Most of these were identified through association studies, but none is currently relevant for genetic testing in clinical practice (AlzGene Database http://www.alzforum.org/res/com/gen/alzgene/default.asp).

Frontotemporal lobar degeneration

The heterogeneous group of frontotemporal lobar degeneration (FTLD) disorders are characterized by predominantly frontotemporal distribution of cortical cerebral atrophy and a clinical picture of prominent behavioral changes, frontal deficits, and/or speech dis-

Table 3 Genetics of hereditary dementias

Disorder	Abbreviation	Mode of inheritance	Gene locus	Mutated protein	Type of mutation	OMIM
Familial Alzheimer's disease	AD1	AD	21q21	Amyloid Precursor Protein	Pm, Dupl	104760
	AD2	AD	19q13.2	ApoE	CV	104310
	AD3	AD	14q24.3	Presenilin 1	Pm, exonic deletions	104311
	AD4	AD	1q31–q42	Presenilin 2	Pm	600759
Frontotemporal dementia with parkinsonism	FTPD-17	AD	17q21	MAPTau	Pm, Del, Ins	601630
Frontotemporal dementia with ubiquitinated lesions	FTD-U	AD	17q21	Progranulin	Pm, genomic Del	607485
Fam. Creutzfeld–Jakob disease	PRNP	AD	20pter-p12	Prion protein	Pm, Ins	123400

AD, autosomal dominant; Pm, point mutation; Del, deletion; Ins, insertion; CV, common variant; MAPTau, microtubule-associated protein tau.

turbances. Consensus criteria have been published and are widely accepted to distinguish three clinical variants. The behavioral variant (bvFTLD or FTD) is also called frontal variant with prominent behavioral disturbances. The two variants with prominent language disorders include semantic dementia (SD, characterized mainly by a fluent dysphasic syndrome) and primary non-fluent aphasia (PNFA). In all of these variants, however, other signs and symptoms of an atypical parkinsonian syndrome (often in the form of a corticobasal syndrome, CBS, or of a syndrome resembling progressive supranuclear palsy, PSP) or motor neuron degeneration (MND) might occur and may even dominate the clinical picture. The most common presentation is an early change in personality, social behavior, and language dysfunction, with relative preservation of memory functions. Historically, at least a subset of these patients had been subsumed under the heading of Pick's disease. Today, the term FTLD is suggested as an umbrella term.

Pathologically, the majority of patients with FTLD show ubiquitinated deposits of the protein TDP-43 (this form has been designated FTLD-TPD). In a substantial proportion of patients, however, deposition of the microtubule-associated protein tau (MAPT) is found; in these patients, the disease is called FTLD-Tau. Further, in a small subset of patients with FTLD-U pathology, the ubiquitinated inclusions are negative for TDP-43 and Tau and consist of an as yet elusive protein composition. A wide spectrum of loss-of-function mutations (haploinsufficiency), often small deletions or insertions leading to a pre-mature stop codon in the progranulin gene (*PGRN*) [23,24], have been found in FTLD-TDP. In contrast, missense or splice-site mutations *MAPT* have been recognized as a cause of FTLD-tau (Table 3).

The relationship between genotype, pathology, and clinical phenotype in FTLD is complex. Clinical features associated with a particular genetic cause or pathology vary widely, even within families. As a general rule, prominent extrapyramidal symptoms are somewhat more likely to predict a tauopathy, whereas behavioral problems and semantic dementia are more likely to predict a TDP-43 proteinopathy [25]. On the other hand, however, parkinsonism was found in 30% of patients with *PGRN* mutations in a large series [26]. The fact that approximately 30–50% of patients with FTLD, depending on the clinical subtype, have a positive family history, suggests autosomal dominant inheritance. The proportion is highest in those with FTD-ALS and lowest in semantic dementia [27]. Mutations in the *MAPT* gene can be found in 10–43% of patients with a positive family history of FTLD but only about 3% of all patients with FTLD. *PGRN* mutations account for 13–26% of familial and 1–11% of all FTLD cases (3.2% in apparently sporadic cases) [28]. Therefore, genetic screening of the *PGRN* and *MAPT* genes is clearly indicated and useful for genetic counseling in patients with autosomal dominant FTLD. It can also be considered in sporadic cases, although mutations are found only in $<10\%$. Other genes associated with familial forms of FTLD include the *CHMP2B* gene on chromosome 3 and the gene for the valosin-containing protein on chromosome 9. In the latter, FTLD is often found in conjunction with an inclusion body myopathy and early-onset Paget's disease. Both of these forms of familial FTLD are very rare.

Prion diseases

Prion diseases (spongiform encephalopathies, in humans usually known as *Creutzfeld–Jakob disease*, *CJD*) are a group of usually rapidly progressive dementias manifesting as idiopathic, acquired, or inherited disorders. A clearly positive family history of a dominant inheritance is found in 10–20% of cases. Numerous different mutations in the prion protein gene on chromosome 20 have been identified in these families (Table 3). Complete sequencing of the prion protein gene is provided by several centers and can be offered, given the appropriate counseling, in cases with a strong clinical suspicion of familial CJD.

Clinical heterogeneity

Occasionally, mutations in genes typically implicated in one neurodegenerative disorder can be identified in patients clinically presenting with another neurodegenerative disorder. Examples include the *MAPT Arg406Trp* mutation associated with Alzheimer's disease phenotype and PSEN1 Gly183Val in a patient with pathologically confirmed Pick disease. Patients with *PGRN* loss-of-function mutations also display a broad phenotypic spectrum. Thus, in a case of negative mutation screening of known genes but a strong indication of familial inheritance, it is recommended to extend the mutation screening to genes implicated in other neurodegenerative diseases.

Recommendations

In the setting of a clinical diagnosis of AD, mutational screening first in *PSEN1*, then in *APP*, and finally (if negative) in *PSEN2* can be useful for genetic counseling in cases of early-onset autosomal dominant AD (level B). Genetic screening in sporadic cases with early onset can be considered (good practice point). If the clinical

diagnosis is that of a frontotemporal dementia, genetic testing for mutations in *PGRN* and *MAPT* is clearly indicated and useful for genetic counseling in patients with autosomal dominant FTLD (level B), regardless of the presence or severity of extrapyramidal features. Testing can also be considered in familial and sporadic cases, although mutations are found only in $< 5\%$ (good practice point).

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