

Practical guidelines for molecular testing in epilepsy

Disease definition : Epilepsy usually results from metabolic or structural defects in the brain. A minority of epilepsy is caused by a single mutation in an epilepsy-associated gene, and referred to as Hereditary non-syndromic epilepsy.

Frequency : Hereditary non-syndromic epilepsy affects approximately 1 in 500 persons.

Main clinical symptoms : Hereditary non-syndromic epilepsy refers to a clinically and genetically very heterogeneous group of neurological disorders characterized by various epileptic manifestations, with or without neurologic, cognitive, and behavioral deterioration. There are numerous forms of epilepsy, subdivided into clinical syndromes on the basis of age of onset, seizure patterns and other clinical, electroencephalographic, and imaging features.

Inheritance : Hereditary non-syndromic epilepsy can be inherited in an autosomal dominant, autosomal recessive or X-linked manner, and can be caused by mutations in more than 30 genes.

Clinical diagnosis : If epilepsy is suspected an electroencephalogram (EEG) should be made.

Clinical classification : The commonest epilepsy syndromes that can be caused by monogenic mutations are :

- febrile seizures (FS)
- generalized epilepsy with febrile seizures plus (GEFS+)
- severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome)

- idiopathic generalised epilepsies (IGE)
- autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)
- autosomal dominant partial epilepsy with auditory features (ADPEAF)
- benign familial neonatal (BFNS), neonatal-infantile (BNIS) and infantile (BFIS) seizures
- childhood (CAE) and juvenile (JAE) absence epilepsy
- episodic ataxia (EA)
- juvenile myoclonic epilepsy (JME) including Lafora and Unverricht and Lundborg epilepsies
- Ohtahara syndrome

Molecular testing : Up to now than 30 genes have been implicated in hereditary non-syndromic epilepsy, which complicates molecular testing. Only in a minority of Hereditary non-syndromic epilepsy a mutation can be identified.

Most mutations are in genes that encode ion channel subunits or membrane receptors. This has led to the concept that the idiopathic epilepsies are a family of channelopathies. The subcategories of genes involved include :

- Sodium channel genes : SCN1A, SCN1B, SCN2A
- Potassium channel genes : KCNQ2, KCNQ3, KCNMA1
- Chloride channel genes : CLCN2
- Calcium channel genes : CACNB4
- GABA receptor genes : GABRG2, GABRA1, GABRD
- Acetylcholine receptor genes : CHRNA4, CHRNB2
- Miscellaneous proteins : ARX, LGI1, CDKL5, STXBP1, ALDH7A1, EPM2A, NHLRC1, CSTB, PCDH19

References

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Deprez L, Jansen A, De Jonghe P. Genetics of epilepsy syndromes starting in the first year of life. *Neurology.* 2009;72:273-281.

Databases

<http://www.carpedb.ua.edu/search.cfm>

Table 1. Different types of Hereditary non-syndromic epilepsy with the respective disease gene, and the size of the gene

Type	Gene	Protein	% Positive	Number of Exons (AA)	Price (Euro)
Pyridoxine-dependent epilepsy	ALDH7A1	Alpha-aminoadipic semialdehyde dehydrogenase	100	18 exons (511 AA)	1000
GEFS	SCN1A	Sodium channel, voltage-gated, type I, alpha	5-10	26 exons (2009 AA)	1820
	SCN1B	Sodium channel subunit beta-1 Precursor	4	6 exons (218 AA)	2100
	GABRG2	Gamma-aminobutyric acid receptor subunit gamma-2 Precursor	1	11 exons (475 AA)	2200
Dravet-SMEI	SCN1A	Sodium channel, voltage-gated, type I, alpha	50	26 exons (2009 AA)	1820
West syndrome (early infantile epileptic encephalopathy, EIEE)	ARX	Aristaless-related homeobox gene	Male patients	5 exons (562 AA)	790
	CDKL5	Cyclin-dependent kinase-like 5	Female patients	23 exons (1030 AA)	1490
Ohtahara syndrome	STXBP1	Syntaxin-binding protein 1		20 exons (603 AA)	
ADPEAF	LGI1	Leucine-rich, glioma inactivated 1	50	8 exons (557 AA)	
BFNS	KCNQ2	Potassium voltage-gated channel subfamily KQT member 2	50	18 exons (880 AA)	1600
	SCN2A	Sodium channel protein type 2 subunit alpha	10	27 exons (2005 AA)	2200
	KCNQ3	Potassium voltage-gated channel subfamily KQT member 3	5	15 exons (872 AA)	
Myoclonic epilepsies (Lafora, Unverricht and Lundborg)	EPM2A	Epilepsy, progressive myoclonus type 2A, Lafora disease	Many	7 exons (331 AA)	650
	NHLRC1	Nhl repeat-containing 1 gene	Many	1 exon (395 AA)	650
	CSTB	Cystatin B	Many	3 exons (98 AA)	400
Idiopathic generalised epilepsies (IGE)	CACNA1H	Voltage-dependent t-type calcium channel subunit alpha-1h	10	33 exons (2353 AA)	
	GABRD	Gamma-aminobutyric acid receptor subunit delta Precursor	Few	9 exons (452 AA)	
	CLCN2	Chloride channel protein 2 (clc-2)	Few	24 exons (898 AA)	
	GABRA1			11 exons (456 AA)	
Absence epilepsies	GABRG2	Gamma-aminobutyric acid receptor subunit gamma-2 Precursor	Few	11 exons (475 AA)	2200
	CLCN2	Chloride channel protein 2 (clc-2)	Few	24 exons (898 AA)	
ADNFLE	CHRNA4	Acetylcholine receptor, neuronal nicotinic, alpha-4 subunit	10	7 exons (627 AA)	1100
	CHRN2	Acetylcholine receptor, neuronal nicotinic, beta-2 subunit	10	6 exons (502 AA)	1250
	CHRNA2	Acetylcholine receptor, neuronal nicotinic, alpha-2 subunit	< 5	8 exons (529 AA)	1250

