Chapter 17
Epilepsy and Genetics

CQ 17-1

Relation between epilepsy and genetics

Summary

When a parent has epilepsy, the frequency of the patient's children developing epilepsy is 4–6%, which is 2–3 times higher than that in the general population. However, the frequency varies depending on the cause of epilepsy. There is no clear pattern of inheritance for epilepsy in general.

Comment

The genetic factor plays a small role in the pathogenesis of epilepsy in general[1]. Therefore, we should take care not to give excessive anxiety to patients and their families and not to lead them to misunderstand the negative impact of the genetic factor.

In some patients, family history reveals definite inheritance patterns (epilepsy syndrome) such as autosomal dominant and recessive inheritance, or sex-linked inheritance. However, the inheritance pattern is undetermined in most of the patients with epilepsy. The familial prevalence and the rate of EEG abnormalities differ even for the same epilepsy syndrome, suggesting multifactorial inheritance pattern involving many overlapping factors. The incidence rate of epilepsy in descendants of the patients is 6%, which is clearly higher than the incidence for people aged up to 20 years in the general population (1–2%). When the mother has epilepsy or when one of the parents has absence seizures, the incidence rate is further increased to 8–9%[2]. In addition, epilepsy occurs relatively frequently in siblings of patients with epilepsy. In the case that the onset age of the proband is under 15 years, the incidence rate of epilepsy in siblings by 20 years of age is 3–5%[2]. Moreover, the incidence rate increases to 5–15% in the proband's siblings when the EEG of the proband shows generalized spike-and-wave complex, or when the proband's parent is (or both parents are) affected by epilepsy[2].

Regarding febrile convulsion, while the prevalence in children is 7–11% (4% in other countries), the prevalence increases to 20–25% in siblings of patients with febrile convulsion. Also, children with febrile convulsion will eventually have non-febrile convulsion (epilepsy) at a higher rate when their parents are affected by epilepsy[3, 4].

■ References

1) Genetics Commission of International League Against Epilepsy. Things you want to know. https://www.ilae.org/files/dmfile/GeneticsPamphlet-2013.pdf
2) Hauser WA, Hesdorffer DC. Facts about epilepsy. New York: Demos press, 1999. p.1-16.
3) Granstrom ML, Gaily E, Beck-Mannagetta G. Febrile convulsions, epileptic seizures and EEG abnormalities in offspring of epileptic mothers. In: Beck-Mannagetta G, Anderson VE, Doose H, Janz D eds. Genetics of epilepsies, Berlin: Springer-Verlag, 1989. p.137-141.
4) Clinical Practice Guideline for Febrile Convulsion Development Committee (ed.), The Japanese Society of Child Neurology (supervision). Clinical Practice Guideline for Febrile Convulsion 2015. Tokyo: Shindan To Chiryou Sha, Inc. 2015 (in Japanese).

■ Search formula and secondary sources for reference

PubMed search: June 28, 2015

No. of references 63 "epilepsy/genetics [majr] AND heredity [mesh] Sort by: Relevance Filters: Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese"

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No. of references 100, ((epilepsy/MTH) and ((genetic test/TH or genetic test/AL))) and (PT = excluding proceedings)

CQ 17-2

Current situation of genetic research and genetic testing for epilepsy

Summary

Various mutations have been identified in many epilepsy syndromes. However, genetic diagnosis has clinical significance in only a few epilepsy syndromes. Identification of gene abnormalities leads to a definite diagnosis only for progressive myoclonic epilepsy, Angelman syndrome, Rett syndrome, and Dravet syndrome.

Comment

The causative genetic abnormalities for various epilepsy syndromes are shown in **Table 1**[1, 2], and those for progressive myoclonic epilepsy (PME) are shown in **Table 2**[3]. When Dravet syndrome is suspected, gene testing is useful because the findings from the SCN1A genetic test may help us determine the treatment strategy and provide genetic counseling at an earlier stage than when diagnosis is obtained from only clinical symptoms[4].

On the other hand, based on the current knowledge about genetic research on epilepsy, genetic results cannot accurately predict the prognosis (for example, patients with the same SCN1A mutation may have different phenotypes). Moreover, even when the genetic test result is negative, it does not exclude the possibility of having an unknown causative gene or a gene unidentifiable by conventional sequence analyses such as copy-number polymorphisms. It should be noted that genetic tests have only limited usefulness for exclusion diagnosis.

Furthermore, many genetic tests are not covered by medical insurance at present, making it difficult to be used as a routine test in the clinical practice.

■ References

1) Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. Epilepsia. 2010; 51(4): 655-670.
2) Ishii A. Molecular genetics of Dravet syndrome and GEFS+ : The spectrum of epilepsies caused by mutations of SCN1A and other genes. Igaku No Ayumi. 2015: 253(7); 561-567 (in Japanese).
3) Nakayama T. Molecular genetics of progressive myoclonic epilepsy. Igaku No Ayumi. 2015: 253(7); 584-588 (in Japanese).
4) Hirose S, Scheffer IE, Marini C, et al. Genetics Commission of the International League Against Epilepsy. SCN1A testing for epilepsy: application in clinical practice. Epilepsia. 2013; 54(5): 946-952.

■ Search formula and secondary sources for reference

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No. of references: 21, "epilepsy/genetics [majr] AND genes [mesh] Filters: Review; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese"
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Table 1. Causative genes identified in various epilepsy syndromes.

Epilepsy syndrome	Locus	Gene	Product
Benign familial neonatal seizures	20q13.3 8q24	*KCNQ2* *KCNQ3*	K_V7.2(K^+ channel) K_V7.3(K^+ channel)
Benign familial neonatal-infantile seizures	2q23-q24.3	*SCN2A*	Na^+ channel α_2 subunit
Benign infantile epilepsy	16p11.2	*PRRT2*	Proline-rich transmembrane protein 2
Ohtahara syndrome	9q34.1 Xp22.13	*STXBP1* *ARX*	Syntaxin binding protein 1 Aristaless related homeobox
Infantile spasms (atypical Rett syndrome / West syndrome)	Xp22	*STK9/CDKL5*	Cyclin-dependent kinase-like 5
X-linked infantile spasms	Xp22.13	*ARX*	Aristaless related homeobox
Severe myoclonic epilepsy of infancy (Dravet syndrome)	2q24 2q24.3 5q34-q35 9q34.1	*SCN1A* *GABRG2* *GABRA1* *CHD2* *STXBP1*	Na^+ channel α_1 subunit $GABA_A$ receptor γ_2 subunit $GABA_A$ receptor α_1 subunit Chromodomain helicase DNA binding protein 2 Syntaxin binding protein 1
Genetic epilepsy with febrile seizures plus (GEFS+)	2q24 19q13.1 5q34	*SCN1A* *SCN1B* *GABRG2* *GABRD* *SCN9A* *STX1B*	Na_v1.1(Na^+ channel) Na^+ channel β_1 subunit $GABA_A$ receptor γ_2 subunit $GABA_A$ receptor δ subunit Na^+ channel α_9 subunit Syntaxin 1B
Childhood absence epilepsy (with febrile seizures plus)	5q34	*GABRG2*	$GABA_A$ receptor γ_2 subunit
PCDH19-related epilepsy limited to females	Xq22	*PCDH19*	Protocadherin 19
Early-onset absence epilepsy (glucose transporter-1 deficiency syndrome)	1p35-p31.1	*SLC2A1*	GLUT1
Juvenile myoclonic epilepsy	5q34-q35 6p12-p11	*GABRA1* *EFHC1*	GABAA receptor α1 subunit EF-hand domain-containing protein 1
Autosomal dominant nocturnal frontal lobe epilepsy	20q13.2-q13.3 1q21 8p21	*CHRNA4* *CHRNB2* *CHRNA2*	nACh receptor α_4 subunit nACh receptor β_2 subunit nACh receptor α_2 subunit
Autosomal dominant lateral temporal epilepsy (autosomal dominant epilepsy with auditory features)	10q24	*LGI1*	Leucine rich glioma inactivated 1
Generalized epilepsy and paroxysmal dyskinesia	10q22	*KCNMA1*	K_{Ca}1.1(K^+ channel)
Absence epilepsy and episodic ataxia type 2	19p13	*CACNA1A*	Ca_v2.1(Ca^{2+} channel)
Focal epilepsy and episodic ataxia type 1	12p13	*KCNA1*	K_v1.1(K^+ channel)
Familial hemiplegic migraine and epilepsy	1p21-23	*ATP1A2*	Sodium-potassium ATPase
Angelman syndrome	15q11-13	Loss including *UBE3A*	(UBE3A)
Rett syndrome	Xp28 14q12	*MECP2* *FOXG1*	Methyl-CpG-binding protein-2 Forkhead box protein G1

(Partially modified from: Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies—report of the ILAE Genetics Commission. Epilepsia. 2010; 51(4): 655-670.)

Table 2. Causative genes in progressive myoclonic epilepsy (PME).

Name of disease	Onset age (years)	Clinical symptoms	Locus	Gene
Neuronal ceroid lipofuscinosis (NCL)*				
			1p34.2	*CNL1*
Infantile NCL	0.5–2	Vision loss, microcephaly, epilepsy, regression	11p15.4	*CNL2*
			16p11.2	*CNL3*
Late Infantile NCL)	2–4	Vision loss, epilepsy, myoclonus	20q13.33	*CNL4*
			13q22.3	*CNL5*
			15q23	*CNL6*
Juvenile NCL	4–10	Vision loss, epilepsy	4q28.2	*CNL7*
			8p23.3	*CNL8*
Adult NCL	12–50	Epilepsy, ataxia, dementia	Not Mapped	*CNL9*
			11p15.5	*CNL10*
			17q21.31	*CNL11*
			11q13.2	*CNL13*
			7q11.21	*CNL14*
Dentatorubral-pallidoluysian atrophy (DRPLA)	All ages	Myoclonus, cerebella ataxia, epilepsy	12p13.31	*ATN1*
Mitochondrial encephalomyopathy (MERRF)	5–42 (mostly in childhood)	Short stature, hearing loss, cardiomyopathy	mtDNA	*MT-TK*
			mtDNA	*MT-TL1*
			mtDNA	*MT-TF*
			mtDNA	*MT-T1*
			13q34	*CARS2*
Unverricht-Lundborg disease (ULD)	6–16	Myoclonus, epilepsy, no or mild intellectual disability	21q22.3	*CSTB*
			12q12	*PRICKL*
			4q21.1	*E1*
			17q21.32	*SCARB2*
				GOSR2
PME with K^+ channel abnormality	6–14	Resembling Unverricht-Lundborg disease	11p15.1	*KCNC1*
Lafora disease	9.5–18	Epilepsy, myoclonus, regression	6q24.3	*EPM2A*
			6p22.3	*EPM2B*

* The loci and responsible genes for NCL are identified from all NCL, and does not correspond to each clinical subcategory.
(Partially modified from: Nakayama T. Molecular genetics of progressive myoclonic epilepsy. Igaku No Ayumi. 2015: 253(7); 584-588.)