

Genetics and Epilepsy

The completion of the human genome project and the further availability of increasingly detailed data on human chromosomes¹ promise much for our understanding of the genetic basis of human health and disease. The entire human genome contains some 30,000 genes, more than half of which are expressed at some stage in the brain. Genetic influences on brain function and diseases are therefore pervasive. In the outbred human species, epilepsy is obviously not a constitutive phenotype: there are certain genetic variants that either directly cause or contribute to epilepsy phenotypes. Epilepsy is a heterogeneous group of conditions, and thus genetic influences on different types of epilepsy are likely to vary widely. However, whilst genes encode every protein, many proteins undergo additional modulation by factors ranging from the post-transcriptional to the macroenvironmental, so that we, and our diseases, are generally not products of a rigid genetic determinism. However, genetic factors are perhaps now more readily determined than environmental factors, so that genetic studies in epilepsy hold promise for a better understanding and more rational treatment than that which currently exists.

Genes could influence seizures, epileptogenesis and epilepsy at multiple levels. Genetic variation could affect the aetiology, susceptibility, mechanisms, syndrome, treatment response, prognosis and consequences of the epilepsies to varying degrees in different individuals. Part of the promise of genetics lies in its power to relate these facets of the overall clinical presentation to the individual patient. There has been considerable recent progress, though this has focused largely on aetiology, susceptibility and treatment response.

More and more genetic mutations are being identified that cause epilepsy. These mutations usually cause conditions that are inherited in a classical Mendelian fashion: autosomal dominant, autosomal recessive, X-linked or through mitochondrial inheritance. Mutations are rare and, even collectively, mutational causes of conditions in which epilepsy is the sole or main manifestation account for only a small proportion of cases of epilepsy. Perhaps unsurprisingly given the central position of neuronal excitability in epilepsy, most mutations so far uncovered that lead to epilepsy occur in genes encoding ion channels.² Sodium, potassium, calcium and chloride channelopathies have all been described, and there are likely to be others to come (Table 1). It is worth noting, in passing, that acquired epileptogenic channelopathies also exist.³ Mutations that cause monogenic epilepsies fall into two other major categories: those that lead to structural brain malformations one clinical manifestation of which is epilepsy;⁴ and those that produce the progressive myoclonic epilepsies (PMEs).⁵ The latter are themselves a diverse group of conditions distinguished by particular natural histories, pathophysiologies and investigational findings, but which broadly share the common characteristics of myoclonic jerks, other seizure types and progressive cognitive decline: many PMEs can now be defined and dissected genetically (Table 2). Only a few other genetic mutations are known to lead to epilepsy as their major consequence. These include LGI1, mutations which cause a familial focal epilepsy.⁶ There are of course a large number of Mendelian conditions with known underlying gene mutations that cause multisystemic conditions in which seizures are part of a broader phenotype: the number of these also continues to grow, but again account for only a small proportion of the epilepsies.

This progress in the genetic aetiology of the epilepsies is remarkable, and as yet unmatched by developments in the genetics of other aspects of disease biology, such as

susceptibility or treatment response, reflecting partly the focus of researchers so far, but also the tractability of the relevant issues.

Genetic variation influencing susceptibility to non-Mendelian epilepsies has been the other major focus of research. Most epilepsies are complex traits and probably arise in individuals as a result of gene-gene and gene-environment interactions. The numbers of genes involved are unknown, and may be few or many. The resulting patterns of inheritance in the majority of cases are thus more complicated and subtle: such inheritance falls outside the Mendelian patterns to which we have become accustomed. As a corollary, large cohorts of patients are needed to extract the risks attributable to particular common genetic variants. Many positive associations between particular gene variants and defined epilepsy syndromes have been found; it is likely that many more negative results have not made it to the editor's in-tray. However, no common genetic variants are yet accepted as genuinely increasing the risk of any particular epilepsy type or syndrome.⁷ Numerous problems of methodology dog this area of research. Perhaps the most important is that any one research centre is unlikely to be able to recruit sufficient numbers of patients with an appropriately homogeneous phenotype to have adequate power to detect individual gene effects which are in practice likely to be minor: a parallel with international clinical trials recruiting thousands to show minor benefits from a new treatment regime may be drawn. However, as our understanding of the genome and its vagaries improves, and with increased experience and international collaboration, it seems likely that common genetic variants driving common disease processes will emerge.

The genetics of drug response may prove to be more amenable to analysis than other aspects of genetics in epilepsy, because the proteins that are drug targets, drug transporters and drug metabolisers are to varying extents already known. Their encoding genes do not need to be picked, at random or otherwise, from 30,000 genes,⁸ and many have been thoroughly characterised.⁹ For example, it is well established that individuals who possess certain alleles of the CYP2C9 gene, that encodes the major metabolising enzyme of phenytoin, have significantly reduced rates of metabolism of phenytoin, necessitating lower maintenance doses,¹⁰ although prospective genotyping is not yet undertaken in practice. Whether variants in the ABCB1 gene, that encodes the broad-spectrum multidrug transporter P-glycoprotein, influence resistance to antiepileptic drugs or not remains a hotly-debated point.^{11,12} Gene variants influencing the sensitivity of targets to antiepileptic drugs are also being uncovered: for example, a splice site variation in the SCN1A gene that encodes the cerebral neuronal target of many antiepileptic drugs, has been associated with dosing of these drugs.¹⁰ Such pharmacogenetic advances, if substantiated by further studies and proven in structured trials to be clinically significant, may permit closer modelling of treatment to the individual patient.

The genetics of most other biological facets of epilepsy have not yet even been considered in any detail, but it remains possible that genetic variation will also have an impact of clinical relevance in these other areas (eg biological consequences of epilepsy in an individual patient). Much is still expected of genetic research: careful evaluation in the clinical setting will remain critical to establishing the practical utility of such research. Close collaboration between epilepsy clinical centres, and between clinical and laboratory scientists, and accurate definition of phenotypes, will be the key to bringing epilepsy genetics to the clinic for the benefit of patients and society.



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Table 1. Genetics of monogenic inherited epilepsies: some selected genetic data

Epileptic Disorder	Mode of Inheritance	Locus	Gene	Protein
Monogenic epileptic syndromes of early life				
<i>Benign familial neonatal convulsions (BFNC)</i>	AD	20q (EBN1)	KCNQ2	Voltage-gated K channel
<i>Benign familial neonatal infantile seizures (BFNIS)</i>	AD	8q (EBN2) 2q	KCNQ3 SCN2A	Voltage-gated K channel $\alpha 2$ subunit of the voltage-gated Na channel
Partial epilepsies				
<i>Autosomal dominant nocturnal frontal-lobe epilepsy</i>	AD	20q13.2 1(pericentromere)	CHRNA4 CHRN2	$\alpha 4$ subunit of nAChR $\beta 2$ subunit of nAChR
<i>Familial lateral temporal-lobe epilepsy with auditory symptoms (ADPEAF)</i>	AD	10q	LGII	Epitempin
Primary generalised epilepsies				
<i>Juvenile myoclonic epilepsy</i>	AD	6p12-11	EFHC1	EFHC1 protein
	AD	6p21.3	Unknown	Unknown
		15q14	Unknown	Unknown
		5q34	GABRA1	$\alpha 1$ subunit of the GABA(A) receptor
<i>Idiopathic generalised epilepsies</i>		3q26	CLCN2	voltage-gated chloride channel
<i>Generalised epilepsy with paroxysmal dystonia</i>	AD	10q22	KCNMA1	Pore-forming α subunit of BK channel
<i>Absence epilepsy with episodic ataxia</i>	AD	19	CACNA1A	Pore-forming α subunit of a calcium channel
Generalised Epilepsy with Febrile Seizures +				
	AD	19q (GEFS+1)	SCN1B	$\beta 1$ subunit of the voltage-gated Na channel
	AD	2q31 (GEFS+2)	SCN1A	$\alpha 1$ subunit of the voltage-gated Na channel
	AD	2q31	SCN2A	$\alpha 2$ subunit of the voltage-gated Na channel
	AD	5q31 (GEFS+3)	GABRG2	$\gamma 2$ subunit of the GABA(A) receptor
Severe Myoclonic Epilepsy of Infancy				
	<i>De novo or transmitted</i>	2q31	SCN1A	$\alpha 1$ subunit of the voltage-gated Na channel
		5q31	GABRG2	$\gamma 2$ subunit of the GABA(A) receptor

Note that additional loci exist for many of these disorders: the table is intended to show examples, and is not comprehensive.

AD=autosomal dominant; AR=autosomal recessive; Na=sodium; K=potassium; nAChR=nicotinic acetylcholine receptor.

Modified and updated after: Gourfinkel-An I, Baulac S, Nabbout R, et al. Monogenic idiopathic epilepsies. *Lancet Neurol* 2004; 3; 209-18 Table 1.

Table 2: Genetics of Progressive Myoclonic Epilepsies

Disorder	Gene	Protein
Neuronal Ceroid Lipofuscinoses		
<i>Infantile</i>	CLN1	Palmitoyl-protein thioesterase 1 (PPT1)
<i>Late Infantile</i>	CLN2	Tripeptidyl peptidase 1 (TPP1)
<i>Finnish variant late infantile</i>	CLN5	Novel membrane protein
<i>Variant late infantile</i>	CLN6	Novel membrane protein
<i>Juvenile</i>	CLN3	Novel membrane protein
<i>Northern epilepsy</i>	CLN8	Novel membrane protein
<i>Adult (Kufs disease)</i>	---	---
Lafora body disease		
	EPM2A	Laforin
	EPM2B (NHLRC1)	Malin
Sialidosis	NEU1	Neuraminidase 1
Unverricht-Lundborg disease		
	CSTB (EPM1)	Cystatin B
	EPM1B	Not known
MERRF	MTTK	tRNALys
Juvenile GM2, gangliosidosis type III	HEXA	β N acetylhexosaminidase A deficiency
DRPLA	DRPLA (triplet repeat disease)	Atrophin 1

Note there are other even more rare PMEs, not included in this table.

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