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Genetic mutations associated with status epilepticus

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ABSTRACT

This paper reports the results of a preliminary search of the literature aimed at identifying the genetic mutations reported to be strongly associated with status epilepticus. Genetic mutations were selected for inclusion if status epilepticus was specifically mentioned as a consequence of the mutation in standard genetic databases or in a case report or review article. Mutations in 122 genes were identified. The genetic mutations identified were found in only rare conditions (sometimes vanishingly rare) and mostly in infants and young children with multiple other handicaps. Most of the genetic mutations can be subdivided into those associated with cortical dysplasias, inborn errors of metabolism, mitochondrial disease, or epileptic encephalopathies and childhood syndromes. There are no identified 'pure status epilepticus genes'. The range of genes underpinning status epilepticus differs in many ways from the range of genes underpinning epilepsy, which suggests that the processes underpinning status epilepticus differ from those underpinning epilepsy. It has been frequently postulated that status epilepticus is the result of a failure of 'seizure termination mechanisms', but the wide variety of genes affecting very diverse biochemical pathways identified in this survey makes any unitary cause unlikely. The genetic influences in status epilepticus are likely to involve a wide range of mechanisms, some related to development, some to cerebral energy production, some to diverse altered biochemical pathways, some to transmitter and membrane function, and some to defects in networks or systems. The fact that many of the identified genes are involved with cerebral development suggests that status epilepticus might often be a system or network phenomenon. To date, there are very few genes identified which are associated with adult-onset status epilepticus (except in those with preexisting neurological damage), and this is disappointing as the cause of many adult-onset status epilepticus cases remains obscure. It has been suggested that idiopathic adult-onset status epilepticus might often have an immunological cause but no gene mutations which relate to immunological mechanisms were identified. Overall, the clinical utility of what is currently known about the genetics of status epilepticus is slight and the findings have had little impact on clinical treatment despite what has been a very large investment in money and time. New genetic technologies may result in the identification of further genes, but if the identified genetic defects confer only minor susceptibility, this is unlikely to influence therapy. It is also important to recognize that genetics has social implications in a way that other areas of science do not.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

In the field of epilepsy, new genetic technologies have the potential to enhance greatly our understanding of the causes and mechanisms of epilepsy. To date, there have been numerous studies exploring the role of genetics in ordinary epilepsy, for instance, in various epilepsy syndromes, rare Mendelian 'pure' epilepsies, and epileptic encephalopathies. However, there has been no study focusing synoptically on the genetics of status epilepticus.

Status epilepticus, however, is potentially an important target for genetic studies. The range of known causes of epilepsy which characteristically result in status epilepticus differs considerably from the range of genes that cause 'ordinary' epilepsy (i.e., epilepsy with nonstatus epilepticus seizures). Furthermore, in lesional status epilepticus, the features of the causative lesions (nature, location, size, etc.) differ in relative terms from those in ordinary lesional epilepsy. Status epilepticus can thus be considered not just a more severe form of an 'ordinary' seizure but also one that involves different networks, pathways, biochemical or physiological processes, and mechanisms. It has been postulated that the mechanisms of status epilepticus include a failure of the normal processes of 'seizure termination', but this seems likely to be an oversimplification.

A study of the genetic causes of those epilepsies characteristically associated with status epilepticus might yield clues to the nature or form

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of these mechanisms. It has been hoped that this will lead to new approaches to treatment. It was for these reasons that this preliminary survey was undertaken, and this paper presents the preliminary findings of an ongoing analysis.

2. Aims and methods

The survey takes the form of a review of the published literature undertaken with the following aims:

(1) To identify genes in which mutations are are strongly associated with status epilepticus
(2) To contrast these genes with genes in which mutations are known to be associated with 'pure' epilepsy.

For the purposes of this survey, the 'gene mutations strongly associated with status epilepticus' are defined as mutations in a gene (a) in which status epilepticus is specifically listed as a symptom in standard genetic databases or (b) in which status epilepticus is specifically mentioned in a case report or review article.

A literature search of the OMIM, GeneCard, NCBI Gene, DisGeNet, Medline, and PubMed databases [1–4] and also bibliographic searches of the reference lists from published literature reviews of the past 5 years [5–48] were conducted for (1). The search terms were 'genetics', 'gene', and 'status epilepticus'. This was not a systematic search, and a degree of subjective evaluation was made by the authors: (a) in focusing on definitive and authoritative reviews only in the bibliographic searches which was therefore selective and (b) in the exclusion of genes on the grounds that status epilepticus was considered a minor or infrequent association.

The list for (2) was taken from Zara [49].

This is a preliminary list from a first-pass search of the literature, and further work is necessary to refine the list.

3. Results

Mutations in 122 genes were identified as being strongly associated with status epilepticus (as defined above). In some of these genes, a variety of different mutations were reported in the same gene. It proved possible to subdivide these genes into the following categories:

(a) Genes with mutations causing malformations of cortical development (cortical dysplasia) or other gross cerebral structural changes (Table 1);
(b) Genes with mutations causing inborn errors of metabolism and other congenital conditions (Table 2);
(c) Mitochondrial genetic defects (Table 3);
(d) Genes associated with early childhood epileptic encephalopathies and idiopathic forms of other childhood epilepsy syndromes (Table 4); and
(e) Genes with mutations in cases occurring without gross structural cerebral disorders, inborn errors of metabolism, early childhood epileptic encephalopathy, or epilepsy syndromes (Table 5).

Some of the genetic defects feature in several different categories, and the categories are not mutually exclusive.

The genes underpinning 'pure epilepsy' are shown in Table 6.

Table 1
Nuclear genes causing cortical dysplasia and other cerebral structural abnormalities reported to be strongly associated with status epilepticus.

	ADAR, *AKT3*, *ARX*, *FOLR1*, *FOXG1*, *GRIN2A*, *KCTD7*, *LYK5*, *MLC1*, *OCLN*, *PAFAH1B1*, *PDYN*, *PNKP*, *PRKCZ*, *QARS*, *RNASEH2A*, *RNASEH2B*, *RNASEH2C*, *SAMHD1*, *SCN1A*, *SCN2A*, *SPTAN1*, *SRPX2*, *STXBP1*, *ST3GAL5*, *TBC1D24*, *TREX1*, *TSC1*, *TSC2*

Table 2
Genes causing inborn errors of metabolism and other congenital conditions reported to be strongly associated with status epilepticus.

Disorders of amino acid metabolism	
D- and L-2-hydroxyglutaric aciduria	*D2HGDH*, *L2HGDH*
D-glyceric academia	*GLYCTK*
Disorder of citric acid metabolism (Krebs cycle)	
Fumaric aciduria	*FH*
Disorder of copper metabolism	
Wilson disease	*ATP7B*
Disorder of creatine metabolism	
Guanidinoacetate methyltransferase deficiency	*GAMT*
Disorder of cytosolic protein synthesis	
Cytosolic glutaminyl-tRNA synthetase	*QARS*
Disorder of fatty acid oxidation	
Combined oxidative phosphorylation deficiency 23	*GTPBP3*
Disorder of cerebral folate transport	
Folate transporter deficiency	*FOLR1*
Disorder of GABA metabolism	
GABA transaminase deficiency	*ABAT*
Disorder of glucose transport	
Glucose transporter 1 deficiency	*SCL2A1*
Disorder of glycosylation	
Asparagine-linked glycosylation defect	*ALG13*
Disorders of lipid storage (NCL — see below)	
Gaucher disease type 3	*GBA*
GM2 gangliosidosis (Tay–Sachs)	*HEXA*
GM2 gangliosidosis (Sandhoff)	*HEXB*
Metachromatic leukodystrophy	*ARSA*
Disorders of purine and pyrimidine metabolism	
Adenylosuccinase deficiency	*ADSL*
Beta-ureidopropionase deficiency	*UPB1*
Disorders of pyridoxine metabolism	
Pyridoxine-dependent epilepsy	*ALDH7A1*
Pyridoxal-5′-phosphate dependent epilepsies	*PNPO*
Disorder of serine synthesis	
Phosphoserine aminotransferase deficiency	*PSAT1*
Urea cycle defects	
Ornithine transcarbamylase deficiency	*OTC*
Citrullinemia type 11	*SLC25A13*
Other disorders (IEMs and other congenital conditions)	
Aicardi–Goutières syndrome 6	*ADAR*
Alexander disease	*GFAP*
Angelman syndrome	*UBE3A*, *MECP2*
Angelman-like syndrome	*CDKL5*
GM3 synthase deficiency	*ST3GAL5*
Menkes disease	*ATP7A*
3-Methylcrotonyl CoA carboxylase 2 deficiency	*MCCC2*
Molybdenum cofactor deficiency (leading to sulfite oxidase deficiency)	*MOCS1*, *MOCS1*, *MOCS3*
Mucopolysaccharidosis type II (MPS2: Hunter syndrome)	*IDS*
1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-1 defects	*PLCB1*
Neuronal ceroid lipofuscinoses types 3 and 6	*CLN3*, *CLN6*
Nonketotic hyperglycinemia	*AMT*, *GLDC*, *GCSH*
Rett syndrome	*FOXG1*, *MECP2*
Sialidosis types 1 and 2	*NEU1*, *PPGB*

4. Discussion

This literature review has shown that it is possible to identify genes in which mutations are strongly associated with status epilepticus (i.e., in which status epilepticus is a characteristic, specific, or common feature). Many different types of mutations are found, including

Table 3
Mitochondrial defects (both mitochondrial and nuclear genes) reported to be strongly associated with status epilepticus.

Mitochondrial genetic defects strongly associated with status epilepticus	
a. Nuclear gene defects	*ADCK3*, *COX10*, *GTPBP3*, *PDHX*, *PDSS2*, *PEO1*, *POLG*, *RRM2B*, *SLC25A13*, *SLC25A22*
b. Mitochondrial gene defects	*MTCO1*, *MTND4*, *MTND4*, *MTTF*, *MTTK*, *MTTH*, *MTTL1*, *MTTS1*, *MTTS2*

Progressive myoclonic epilepsies due to mitochondrial disease are discussed below (under syndromes).