Epilepsy Ontology

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ICARE Ontology, considerations

- ICARE has been extremely valuable tool to the American Epilepsy Society in assessing the AES-funded research and visualizing where funds is allotted to.
- Discussions for possible updates of the ontology were prompted by realizing its utility and potential to evaluate funded research and recognizing that:
  - Current ontology terms were not encompassing all research areas and epilepsy/seizure types, etiologies.
  - Interim revisions in the working classification and coding of human epilepsies and seizures.
  - Distinction of human vs nonhuman, basic vs translational research is not easily/accurately derived from the current system. Having this would be very useful (different funding, design, expectations and expertise; could allow faster tracking of experts in clinical vs preclinical translational and basic science research).
  - Use of certain terms in various platforms (ICARE, Benchmarks, researchers) occasionally is done with variable meaning and could benefit of refinement.
  - Enhancement of the capability to query the database with more specific questions would greatly enhance strategic funding decisions and collaborations, attract more organizations to participate in ICARE and possibly eventually compare funded research to publications.
ADEAF - Autosomal Dominant Epilepsy with Auditory Features
ADNFLE - Autosomal-Dominant Nocturnal Frontal Lobe Epilepsy
Alpers Syndrome
Angelman Syndrome
BECTS - Benign Epilepsy with Centrotemporal Spikes
BFNE - Benign Familial Neonatal Epilepsy
CAE - Childhood Absence Epilepsy
Catamenial Seizures
Childhood Epilepsy
Dravet Syndrome
Early Life Seizures
EME - Early Myoclonic Encephalopathy
Encephalitis Acquired Epilepsy
Epilepsy/Seizures associated with other disorders (like Alzheimer’s, Autism, Fragile X, Malaria, ...)
Epilepsy/Seizures in pregnant women
Epilepsy/Seizures in the elderly
Epileptic Encephalopathies
Febrile Seizures
Focal Epilepsy
GEFS+ - Generalized Epilepsy with Febrile Seizures plus
Genetic Epilepsy
Hemiconvulsion–Hemiplegia–Epilepsy
Hypothalamic Hamartoma with Gelastic Seizures
IS - Infantile Spasms
JAE - Juvenile Absence Epilepsy
JME - Juvenile Myoclonic Epilepsy
KCNQ2 Encephalopathy
Lafora Disease
LGS - Lennox-Gastaut Syndrome
LKS - Landau-Kleffner syndrome
Malformations of Cortical Development
Neonatal Seizures
Neurocysticercosis
Nodding Syndrome
Non-Epileptic Seizures
Ohtahara Syndrome
PCDH19 Epilepsy
PME - Progressive Myoclonus Epilepsies
PMSE - Polyhydramnios, Megalencephaly and Symptomatic Epilepsy Syndrome
PTE - Post Traumatic Epilepsy
Rasmussen Syndrome
Reflex Epilepsies
Seizures
Status Epilepticus
Sturge-Weber Syndrome
Succinic Semialdehyde Dehydrogenase Deficiency
SUDEP
TLE - Temporal Lobe Epilepsy
TSC - Tuberous Sclerosis Complex
West Syndrome
Epilepsy - not otherwise specified

Lafora Disease
LGS - Lennox-Gastaut Syndrome
LKS - Landau-Kleffner syndrome
Malformations of Cortical Development
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ICARE Search
ICARE search terms and classifications

**Your search criteria:** FULL TEXT: epileptogenesis

**Further refine search results**
- Funding Year (FY)
  - 2013 (202)
  - 2014 (220)
  - 2015 (208)
  - 2016 (208)

**Funding Agency**
- NIH (640)
- CURE (76)
- AES (35)
- Veterans Affairs (35)
- Dravet Syndrome Foundation (11)
- Phelan-McDermid Syndrome Foundation (11)
- DOD (10)
- EF (7)
- TS Alliance (8)
- Wishes for Elliott (2)
- Batten Disease Support and Research Association (1)
- LGS Foundation (1)
- PCORI (1)

**Distribution of Funding by Benchmark**

- **Early Detection / Diagnosis / Prognosis (76)**
- **Etiology (25)**
- **Mechanism of Disease (537)**
- **Model Systems (76)**
- **Outcomes (11)**
- **Prevention (17)**
- **Treatment (84)**

**Condition**
- TLE - Temporal Lobe Epilepsy (163)
- PTE - Post Traumatic Epilepsy (249)
- Epilepsy - not otherwise specified (117)
- Genetic Epilepsy (60)
- Dravet Syndrome (43)
- Epileptic Encephalopathies (50)
- Epilepsy/Seizures associated with other disorders (like Alzheimer's, Autism, Fragile X, Malaria, ...) (28)
- TSC - Tuberous Sclerosis

**Funding by Research Classification**

- Early Detection: $1,231,091
- Etiology: $4,455,517
- Mechanism of Disease: $1,478,285
- Model Systems: $4,492,022
- Outcomes: $1,628,975
- Prevention: $20,678,301
- Treatment: $1,231,091

**Total Funding by Organization**

- **AES**: $1,242,417
- **CURE**: $3,285,137
- **DOD**: $19,944,044
- **EF**: $746,500
- **Batten Disease Support and Research Association**: $222,150
- **LGS Foundation**: $310,000
- **NIH**: $21,231,091

**Benchmark**

- I. Understand the causes of the epilepsies (55)
- II. Prevent epilepsy and its progression (702)
- III. Improve treatment options (75)
- IV. Limit or prevent adverse consequences (20)
- Not Applicable (5)
<table>
<thead>
<tr>
<th>Research Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>Basic research is the systematic study of the fundamental aspects of phenomena and of observable facts without specific development of processes, products or clinical applications. Projects typically include studies of the mechanisms of normal or disease related processes at the molecular, cellular, systems or organ level.</td>
</tr>
<tr>
<td>Translational</td>
<td>Translational research is the process of developing ideas, insights, and discoveries generated through basic scientific inquiry for the treatment or prevention of human disease.</td>
</tr>
<tr>
<td>Clinical</td>
<td>Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research typically includes therapeutic interventions and applications of new technologies, clinical trials, epidemiologic and behavioral studies, outcomes research and health services research.</td>
</tr>
</tbody>
</table>

1. **Separating research in humans vs in animals / models**

   **Issues:**
   - Basic and translational research may utilize animal/model systems or human subjects which may confound the reporting of funded research in each of these categories.
   - Research using human tissue is not always clinical.
   - Using only keywords for search for human vs animal/model research may not sufficiently differentiate the two different types of research (keyword hits are not always specific for keywords).

   **Suggestions:**
   Separating the two types of research may help visualize and compare more directly:
   - the value, productivity, and results of animal/model vs human epilepsy research
   - Expertise in animal vs human research
   ➔ Suggest to create Refine Search Criteria for:
     - **Organism/Model:**
       - Nonhuman organism
       - Human
       - Other model system
2. Improving distinction of basic and translational research

**Issues:**
Expectations from basic vs translational (preclinical) research may be different in terms of grant review, study design and performance.

Distinction is not always clear producing overlap of hits when using the current system.

**Suggestions:**
→ May consider more specific definitions of how to differentiate and log basic vs translational research.
# Research classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Research included in this category aims to identify the causes or origins of epilepsy - genetic, infectious, metabolic, environmental, or other factors, and the interactions between these factors.</td>
</tr>
<tr>
<td>Mechanism of Disease</td>
<td>Research included in this category looks at the biology of how epilepsy/seizures starts and progresses as well as normal biology relevant to these processes.</td>
</tr>
<tr>
<td>Prevention</td>
<td>Research included in this category looks at identifying interventions which reduce the risk of developing epilepsy by reducing exposure to risk factors and/or increasing protective factors. Interventions aimed at prevention of complications of epilepsy or its co-occurring conditions may also be included. Interventions may target lifestyle or may involve drugs or vaccines.</td>
</tr>
<tr>
<td>Early Detection/ Diagnosis/Prognosis</td>
<td>Research included in this category focuses on identifying and testing biomarkers, technology methods or predictive models that are helpful in detecting and/or diagnosing as well as predicting the outcome or chance of recurrence.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Research included in this category focuses on identifying and testing treatments, such as novel therapeutics, devices or other interventions.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Research included in this category includes a broad range of areas: surveillance and epidemiology; ethics, education and communication approaches for health care professionals, patients and families, and community members; patient care and health care services research; effectiveness research and phase 4 trials.</td>
</tr>
<tr>
<td>Model Systems</td>
<td>Research included in this category looks at the development of new animal models, cell cultures and computer simulations and their application to other studies across the spectrum of epilepsy research.</td>
</tr>
</tbody>
</table>
Research Classification

*Same terms across ICARE, Epilepsy benchmarks epilepsy researchers are not used with the same meaning*

**Examples:**

Prevention of epilepsy / co—occurring conditions and consequences:
- ICARE: intervention-oriented research.
- Benchmarks
  - II: includes mechanisms, biomarkers, interventions
  - I, III and IV: may also address prevention
Prevention research, AES-funded

Prevention Research: ~145K

Benchmark II: ~837.5K

Benchmark IV: ~461K
Benchmark II funded research: Prevent epilepsy and its progression (2016) → no hits for prevention
Research Classification

Same terms across ICARE, Epilepsy benchmarks and in epilepsy research are not always used with the same meaning

Example: prevention of epilepsy / co—occurring conditions and consequences:
- ICARE: intervention-oriented research
- Epilepsy Benchmarks
  - II: includes mechanisms, biomarkers, interventions
  - III and IV: may also address prevention
- Search hits may not always capture the research classification done, as coded

Suggestions:
→ Recoding may probably not be the best solution, since each coding method has its advantages and different information
→ Perhaps:
  → More specific terms coding research classification to track key areas of prevention research (e.g, anti-epileptogenesis, disease modification, etc) ?
  → Refining search tools by allowing to select or exclude classifications or search keywords (AND, OR, NOT) ?
SYNDROMES
Dravet Syndrome
EME - Early Myoclonic Encephalopathy
Epileptic Encephalopathies
Hemiconvulsion–Hemiplegia–Epilepsy
IS - Infantile Spasms
West syndrome
LGS - Lennox -Gastaut Syndrome
LKS - Landau Kleffner syndrome
Ohtahara Syndrome
PTE - Post Traumatic Epilepsy
Rasmussen Syndrome
Nodding Syndrome

SEIZURES
Epilepsy/Seizures associated with other disorders (like Alzheimer's, Autism, Fragile X, Malaria, ...)
Febrile Seizures
Non-Epileptic Seizures
Seizures
Status Epilepticus

SPECIAL POPULATIONS
Early Life Seizures
Neonatal Seizures
Childhood Epilepsy
Epilepsy/Seizures in pregnant women
Catamenial Seizures
Epilepsy/Seizures in the elderly

CONSEQUENCES
SUDEP
Condition: Current epilepsy ontology

GENETIC or GENETIC-STRUCTURAL

Genetic Epilepsy
ADEAF - Autosomal Dominant Epilepsy with Auditory Features
ADNFLE - Autosomal-Dominant Nocturnal Frontal Lobe Epilepsy
BECTS - Benign Epilepsy with Centrocortical Spikes
BFNE - Benign Familial Neonatal Epilepsy
CAE - Childhood Absence Epilepsy
KCNQ2 Encephalopathy
Lafora Disease
PCDH19 Epilepsy
TSC - Tuberous Sclerosis Complex
PME - Progressive Myoclonus Epilepsies
PMSE – Polyhydramnios, Megalencephaly and Symptomatic Epilepsy

ACQUIRED

Encephalitis Acquired Epilepsy
Hypothalamic Hamartoma with Gelastic Seizures

FOCAL vs GENERALIZED

Focal Epilepsy
TLE - Temporal Lobe Epilepsy

OTHER EPILEPSIES

Epilepsy - not otherwise specified
Epilepsy/Seizures associated with other disorders (like Alzheimer's, Autism, Fragile X, Malaria, ...)

ETIOLOGY

Malformations of Cortical Development
Neurocysticercosis
Succinic Semialdehyde Dehydrogenase Deficiency

Not complete list of epilepsies or etiologies

• Only TLE among focal epilepsies
• Focal but no generalized epilepsy coding

Some epilepsies are represented by specific etiologies only, eg
• ADNFLE (no FLE)

Etiologies are not systematically captured or listed in the same manner, eg
• metabolic etiologies
• neurocysticercosis vs epilepsy/seizures associated with other disorders

Some names have been revised or may have additional variations of names, eg
• benign vs self-limited
• GEFS+: Genetic...

No coding for comorbidities, co-occurring conditions
ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology

Ingrid E. Scheffer, Samuel Berkovic, Giuseppe Capovilla, Mary B. Connolly, Jacqueline French, Laura Guilhoto, Edouard Hirsch, Satish Jain, Gary W. Mathern, Solomon L. Moshe, Douglas R. Nordli, Emilio Perucca, Torbjorn Tomson, Samuel Wiebe, Yue-Hua Zhang, and Sameer M. Zuberi

Epilepsia, 58(4):512–521, 2017
doi: 10.1111/epi.13709

Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology


Epilepsia, 58(4):522–530, 2017
doi: 10.1111/epi.13670

ILAE 2017 Classification of Seizure Types Expanded Version

![Diagram of seizure types and epilepsy syndromes]

- **Seizure types**: Focal, Generalized, Unknown
  - **Etiology**: Structural, Genetic, Infectious, Metabolic, Immune, Unknown
  - **Co-morbidities**: Focal, Generalized, Combined Generalized & Focal, Unknown
  - **Epilepsy Syndromes**: Focal, Generalized, Combined Generalized & Focal, Unknown

**Classification of the Epilepsies**

- **Focal Onset**: Awareness, Motor (tonic-clonic, clonic, myoclonic, myoclonic-clonic, myoclonic-tonic-clonic, myoclonic-tonic-atonic, atonic), Nonmotor (absence, typical, atypical, myoclonic, eyelid myoclonia)
  - **Motor Onset**: Automatisms (atonic, clonic, epileptic spasms), Hyperkinetic, Myoclonic, Tonic
  - **Nonmotor Onset**: Autonomic, Cognitive, Emotional, Sensory

- **Generalized Onset**: Tonic-clonic

- **Unknown Onset**: Motor (tonic-clonic, epileptic spasms), Nonmotor (behavior arrest), Unclassified

- **Epilepsy Syndromes**: Focal to bilateral tonic-clonic
The ILAE Commission on Classification and Terminology is pleased to announce the release of EpilepsyDiagnosis.org a cutting-edge online diagnostic manual of the epilepsies.

Manual Goal:
The goal of EpilepsyDiagnosis.org is to make available, in an easy to understand form, the latest concepts relating to seizures and the epilepsies. The principal goal is to assist clinicians who look after people with epilepsy anywhere in the world to diagnose seizure type(s), classify epilepsy, diagnose epilepsy...
Most of the funded research addresses mechanisms / etiologies and yet the codes for such research are minimal and not systematically captured.

→ Suggest adding a crude sub-classification for:

"Etiology":
- Genetic
- Infection
- Immune
- Structural
- Metabolic
- Other

Although these can be searched with keywords, adding this research classification may allow for (a) more specific search, (b) capturing epilepsies in these broader categories, when it may become too complex to add codes for all the specific causes.
Condition: proposal for update

- Etiology
  - Genetic
  - Infection
  - Immune
  - Structural
  - Metabolic
  - Associated with other disorders
  - Other

- Etiology
  - Epilepsy
  - Seizure
  - Epilepsy syndrome

- Onset
  - Focal
  - Generalized
  - Combined
  - Unknown

- Onset
  - Localized
    - Frontal
    - Parietal
    - Occipital
    - Temporal
    - Multifocal
    - Generalized

- Populations
  - Neonatal/Infantile
  - Childhood
  - Adolescent/Adult
  - Special populations
  - Other

- Co-occurring condition
  - Cognitive
  - Behavioral
  - Affective
  - Endocrine
  - Other

- Consequences
  - SUDEP
  - Fetal/neonatal development
  - Quality of life
  - Other

- Epilepsy imitators
  - Syncope and anoxic seizures
  - Behavioral / Psychological and Psychiatric disorders
  - Sleep related conditions
  - Paroxysmal movement disorders
  - Migraine associated disorders
  - Miscellaneous events
Epilepsies / Seizures / Syndromes by Population

NEONATAL/INFANTILE
Self-limited neonatal seizures
  Self-limited familial neonatal epilepsy
Self-limited familial and non-familial infantile epilepsy
EME – Early myoclonic epilepsy
Ohtahara syndrome
West syndrome
Dravet syndrome
Myoclonic epilepsy in infancy
Epilepsy in infancy with migrating focal seizures
Myoclonic encephalopathy in non progressive disorders
Febrile seizures plus, genetic epilepsy with febrile seizures plus
Febrile seizures

CHILDHOOD
Epilepsy with myoclonic-atactic seizures
Epilepsy with eyelid myoclonias
Lennox-Gastaut syndrome
CAE - Childhood absence epilepsy
Epilepsy with myoclonic absences
Panayiotopoulos syndrome
Childhood occipital epilepsy (Gastaut syndrome)
Photosensitive occipital lobe epilepsy
BECTS - Childhood epilepsy with centrotemporal spikes
Atypical childhood epilepsy with centrotemporal spikes
Epileptic encephalopathy with continuous spike-and-wave during sleep
LKS – Landau Kleffner syndrome
Autosomal dominant nocturnal frontal lobe epilepsy

In blue: updates / revisions from existing ontology
Epilepsies / Seizures / Syndromes by Population

**ADOLESCENT / ADULT**
- JAE – Juvenile absence epilepsy
- JME – Juvenile myoclonic epilepsy
- FAME – Familial adult onset myoclonic epilepsy
- Epilepsy with generalized tonic-clonic seizures alone
- Autosomal dominant epilepsy with auditory features
- Other familial temporal lobe epilepsies

**SPECIAL POPULATIONS**
- Early Life
- Neonatal / Infantile
- Childhood
- Pregnant women
- Catamenial
- Elderly

**OTHER**
- Familial focal epilepsy with variable foci
- Reflex epilepsies
- PME - Progressive myoclonus epilepsies
- Epilepsy not otherwise specified
- Seizures
- Status epilepticus
- Nonepileptic events / seizures

*In blue: updates / revisions from existing ontology*
Genetic epilepsies

EPILEPSIES BY ETIOLOGY
Genetic - Chromosomal

15q13.3 MICRODELETION SYNDROME
18q- SYNDROME
INV-DUP (15) OR IDIC (15)
DEL 1p36
ANGELMAN SYNDROME
DOWN SYNDROME (TRISOMY 21)
KLEINFELTERS SYNDROME (XXY)
mILLER DIEKER SYNDROME (DEL 17p)
PALLISTER KILLIAN SYNDROME (TETRASOMY 12p)
RING 14 (r14) SYNDROME
RING 20 (r20) SYNDROME
TRISOMY 12p
WOLF-HIRSCHHORN SYNDROME (DEL 4p)

Genetic - Gene abnormalities

AKT3
ARFGEF2
ARHGEF9
ARX
CACNA1A
CACNB4
CDKL5
CHD2
CHRNA2
CHRNA4
CHRNB2
CLCN2
COL4A1
DCX
DEPDC5
EFHC1
FKTN
FLNA
FMR1 (FRAGILE X SYNDROME)
FOXG1
GABRA1
GABRD
GABRG2
GLI3
GNAQ
GRIN2A
KCNO2
KCNO3
KCNT1
LARGE
LG1
LIS1
MECP2
NPRL3
PCDH19
PIK3CA
PIK3R2
PLCB1
PNKP
POMT1
POMT2
PRRT2
RELN
SCN1A
SCN1B
SCN2A
SLC2A1
SLC25A22
SPTAN1
STXB1
TBC1D24
TCF4 (PITT)

(from https://www.ilae.org/education/diagnostic-manual/epilepsydiagnosis-org)
By Etiology

Structural –
Malformation of cortical development
Vascular malformations
Hippocampal sclerosis
Hypoxic-ischemic
Traumatic brain injury
Tumors
Porencephalic cyst

Metabolic –
Biotinidase and holocarboxylase synthase deficiency
Cerebral folate deficiency
Creatine disorders
Folinic acid responsive seizures
Glucose transporter 1 (GLUT1) deficiency
Mitochondrial disorders
Peroxisomal disorders
Pyridoxine dependent epilepsy / PNPO deficiency

Immune –
Rasmussen’s
Antibody mediated
  Anti-NMDA receptor
  Voltage gated potassium channel
  GAD65 antibody
  GABAB receptor antibody
  Steroid responsive encephalopathy with thyroid disease
  Celiac disease, epilepsy and cerebral calcification syndrome
  Other

Infectious –
Bacterial meningitis or meningoencephalitis
Malaria
Cerebral Toxoplasmosis
CMV
HIV
Neurocysticercosis
Tuberculosis
Viral encephalitis
Other (Lyme disease, toxocariosis, schistosomiasis)

Associated with other diseases
(Alzheimer’s, Autism, Fragile X, Rett syndrome, Malaria, etc)

Unknown
Febrile infection related epilepsy
Considerations

• The coding is oriented towards human classifications of epilepsies / seizures.

• Working classification for animal models of seizures and epilepsies is in progress (ILAE/AES Joint Translational Task Force) and could be considered in the future.

• New revised terms could be added as alternatives / equivalent to existing ones so as not to revise coding from past years.

• It would be useful, if easily feasible, to allow:
  • multiple choices of ontology terms from same categories or keywords
  • enhanced search tools allowing direct comparisons, head to head, of data from various search keywords.

This additional search flexibility could minimize the need in the future for ontology revisions.
Thank you!

- AES
- Eileen Murray
- Penny Dacks
- AES Research & Training Council