Epilepsy Genetics – The NIH/NINDS Perspective

Cleveland Clinic Epilepsy Genetics 2020

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Epilepsy Genetics: Two Categories

- Genes and loci discovered in association with primary epilepsy syndromes, in which the epilepsy is a primary presenting feature

- Genes discovered in association with disorders of brain development that are associated with epilepsy

Epilepsy Genetics

- Diverse and heterogeneous, epilepsy is considered a highly genetic and in many cases heritable condition
NIH Approach to Funding for Epilepsy Research

- Guided by Epilepsy Research Benchmarks
  - First developed by epilepsy research community following Curing Epilepsy Conference in 2000
  - Updated and revised every 7 years in conjunction with an NINDS-sponsored conference
  - Next conference will be a virtual conference on January 4-6, 2021
  - Crowdsourcing exercise launched on September 8, 2020 to get broad input from community
    - Revised Epilepsy Research Benchmarks
    - Transformative Research Priorities
NIH Funding for Epilepsy Research

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Total Funding (In Millions USD)</th>
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<tbody>
<tr>
<td>FY16</td>
<td>$153</td>
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<tr>
<td>FY17</td>
<td>$154</td>
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<td>FY18</td>
<td>$184</td>
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<td>FY19</td>
<td>$188</td>
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<tr>
<td>ESTIMATED FY20</td>
<td>$203</td>
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Funding for Rare and Genetic Epilepsies

• >80% of NIH funding for epilepsy research supports investigator-initiated research grant awards

• Approximately 40% of NIH epilepsy research funding in FY2018 was for research on the rare and genetic epilepsies

• Majority of funding by NINDS, with funding from NCATS, NIA, NIMH, NICHD, NHLBI, NINR and NCCIH
• Epilepsy Phenome Genome Project (EPGP)
  – 1U01NS053998
  – PI: Daniel Lowenstein
• Collected detailed, high quality phenotypic information on 4,199 individuals with epilepsy and their family members
• See: https://www.epgp.org/
Epi4K and Beyond

- Epi4K Center Without Walls
  - Primary goal to increase understanding of the genetic basis of human epilepsy in order to improve the well-being of patients and family members living with these disorders
  - U01NS077276
  - PIs: David Goldstein, Dan Lowenstein, Sam Berkovic
  - Multidisciplinary team science approach to the identification of epilepsy genes
  - Utilized cohorts characterized in EPGP
  - Epi4K Data Browser: http://epi4kdb.org/

- International Consortium: Epi25
  - Collaboration with Broad Institute to sequence 25,000 individuals with epilepsy supported by NHGRI
  - Collaborative of more than 200 partners from 40 research cohorts from around the world
  - 14,000 genomes sequenced to date
  - http://epi-25.org/
On to functional studies!

Two Epilepsy Centers Without Walls

Channelopathy-associated Epilepsy Research Center

- Channelopathy-Associated Epilepsy Research Center
  - U54 NS108874-02S1
  - PI: Alfred George
  - [https://epilepsy-channelopathy.org/](https://epilepsy-channelopathy.org/)

New Center Without Walls – September 1, 2020

- Epilepsy Multiplatform Variant Prediction (EpiMVP)
  - U54 NS117170-01
  - PIs: Lori Isom & Jack Parent
Investigator-Initiated Basic Science Research

- Genetic epilepsies – basic, translational and clinical research
- Somatic mosaicism
- Non-lesional studies of genetic basis of epilepsy
- Animal model development, characterization and drug screening
- iPSCs and organoids

False color image of a slice of human brain organoid from a patient with autism spectrum disorder. Photo by Alysson Muotri, UC San Diego Health
Translational Research Programs

• **Epilepsy Therapy Screening Program (ETSP)**
  – Resources for compound-screening service to identify candidate therapeutics to ameliorate the epilepsies

• **Innovation Grants to Nurture Initial Translational Efforts (IGNITE) Program**
  – Support moving innovative basic science findings to initiate preclinical drug discovery and development

• **Neuroscience Biomarker Program**
  – Supports analytical and clinical validation of candidate biomarkers for neurological disease

• **Blueprint Neurotherapeutics Network (BPN) Program**
  – Support small molecule drug discovery and development

• **Cooperative Research to Enable and Advance Translational Enterprises (CREATE Bio)**
  – Support discovery and development of therapeutic Biotechnology Products and Biologics (e.g. peptides, proteins, oligonucleotides, gene therapies, and cell therapies)

• **Translational Devices**
  – Support development, validation and verification, and early clinical studies of therapeutic devices to treat neurological disorders

• **Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR)**
  – Support small business concerns to conduct innovative neuroscience research at different stages of development, including applied bench research, translational research, and early-stage clinical trials
• Advance medical research on rare diseases
• Provide support for clinical studies and facilitate collaboration, study enrollment and data sharing
• Physician scientists and their multi-disciplinary teams work together with patient advocacy groups to study more than 200 rare diseases at sites across the nation.
• 20 consortia currently funded
• Developmental Synaptopathies Associated with \textit{TSC, PTEN} and \textit{SHANK3} Mutations
• PI: Mustafa Sahin

https://ncats.nih.gov/rdcrn
ClinGen/ClinVar

ClinGen’s Critical Questions

- Is this gene associated with a disease? *Clinical Validity*
- Is this variant causative? *Pathogenicity*
- Is this information actionable? *Clinical Utility*

Building a Genomic Knowledge Base
*ClinVar & Other Resources*

Improved Patient Care Through Genomic Medicine
• The Clinical Genome Resource (ClinGen)
  – Share genomic and phenotypic data between clinicians, researchers, and patients through centralized and federated databases for clinical and research use.
  – Develop and implement standards to support clinical annotation and interpretation of genes and variants.
  – Develop data standards, software infrastructure and computational approaches to enable curation at scale and facilitate integration into healthcare delivery.
  – Enhance and accelerate expert review of the clinical relevance of genes and variants.
  – Disseminate and integrate ClinGen knowledge and resources to the broader community.

ClinGen/ClinVar

- **ClinVar**
  - Facilitate evaluation of variation-phenotype relationships by archiving submitted interpretations of these relationships with supporting evidence
  - Aggregates data from multiple groups to determine if there is consensus about the interpretation
  - Provide access to free summary data
Clinical Trial Readiness

- Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases
  - Support clinical studies to fill gaps in the design of upcoming clinical trials in rare neurological or neuromuscular diseases
  - Validate clinical outcome measures or biomarkers, and/or
  - Characterize cohorts of relevant patients
  - Accelerate initiation of clinical trials for rare diseases and increase the likelihood of success in the trials
- PAR-16-020
Clinical Trials and Networks

• Division of Clinical Research provides funding and oversight for clinical trials to test:
  – Safety and efficacy of innovative treatments of neurological disorders and stroke
  – Epidemiological studies of natural history
  – Biomarker studies
  – Studies designed to elucidate the causes of neurological disorders

Thank you!

Epilepsy Information Page

https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page

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