Genetics Commission

2021 Annual Report

2017 – 2021 Members

Holger Lerche (Germany), chair
Dan Lowenstein (USA), past chair
Piero Perucca (Australia), secretary
Annapurna Poduri (USA)
J Helen Cross (UK), Management Committee liaison

Purpose

- To elucidate the genetic architecture of the epilepsies on a worldwide scale, through large multicenter collaborative frameworks and broad participation by members of ILAE chapters
- To make the results of genetic research readily accessible to clinicians
- To improve the public understanding and knowledge of epilepsy genetics across the world
- To work with related ILAE Commissions to improve education around epilepsy genetics

Activities

We have had three Zoom meetings involving the members of the Genetics Commission and the chairs of the associated Task Forces in May, July and November. These meetings coordinated the activities of the different Task Forces through discussions between the Genetics Commission chair and members, and the elected Task Force chairs. The November meeting was a joint meeting of the old and new (2021 – 2025) Commission. The new Commission decided to continue all activities from the previous term. The only exception has been the creation of a new Task Force on Clinical Genetic Testing in the Epilepsies, led by Dr. Andreas Brunklaus and Dr. Gaetan Lesca, which will follow on the work of the previous one. The new Genetics Commission will continue to carry out the meetings as previously done, together with the associated Task Force leaders.

Budget

We have obtained funds for ongoing support of the Sequencing Data Sharing initiative.

Task Force on Clinical Genetic Testing in the Epilepsies

(Initiated together with the ILAE Diagnostics Commission)

2017 – 2021 Members

Sanjay Sisodiya (UK), chair
Hande Caglayan (Turkey)
Katie Helbig (USA)
Michael Hildebrand (Australia)
Johannes Lemke (Germany)
Piero Perucca (Australia)

Annapurna Poduri (USA)
Lynette Sadleir (New Zealand)
Gagandeep Singh (India)
Yvonne Weber (Germany)
Sarah Weckhuysen (Belgium)

The Task Force has been working on three manuscripts, seeking to raise awareness and provide information on all these knowledge gaps. As a joint effort from the Commission and the Task Force on Clinical Genetic Testing, a manuscript entitled 'Current practice in diagnostic genetic testing in the epilepsies' has been accepted for publication (Krey et al., *Epileptic Disorders*, in press). The other two manuscripts will not be progressed by the Task Force and have been discussed with the new chair.

Genetic Literacy Task Force

2017 – 2021 Members

Nigel Tan (Singapore), co-chair
Dan Lowenstein (USA), co-chair
Sam Berkovic (Australia)
Peter de Jonghe (Belgium)
Ingo Helbig (Germany)
Jiang Yuwu (China)
J Helen Cross (UK), MC liaison

The Task Force's work continued, and we have just published the next paper in the Genetic Literacy series in *Epileptic Disorders* – the paper on Familial Focal Epilepsies. We are planning subsequent papers on Genetic Counselling, Self Limiting Familial Epilepsy Syndromes and SUDEP, and the authors are currently planning their outlines. We continue to maintain the online MCQ website (sample quiz) so that readers can do self-learning immediately after reading, or days/weeks later to refresh their knowledge.

Epilepsiome Task Force

2017 – 2021 Members

Ingo Helbig (USA), co-chair
Heather Mefford (USA), co-chair
Ahmad Abou Tayoun (USA)
Roland Krause (Luxembourg)
Kannan Lakshminarayanan (India)
Nigel Tan (Singapore)
Yi Wang (China)
J Helen Cross (UK), MC liaison

2017 – 2021 Junior Members

David Lewis Smith (UK)
Ganna Balagura (Italy)
Hugh Kearney (Ireland)
Gordon Jing (China)

The Epilepsiome Task Force has continued to approach critical tasks relevant to connecting the clinical epilepsy community with the diagnostic arena and revising the language used in the digital space in accordance with the 2017 ILAE diagnostic criteria. The backbone of the Task Force is the 'Epilepsiome blog', which remains the most frequently read resource for epilepsy and genes with up to 10,000 unique visitors per month.

Another important activity of the Task Force has been gene curation, which has been carried in collaboration with the ClinGen Epilepsy Clinical Domain Working Group. Gene curation has been completed for 71 genes and 82 gene-disease associations. Once completed, the final classification of each gene is published on the freely accessible ClinGen site. A Variant

Curation Expert Panel has been established with funding from NIH to review criteria to establish pathogenicity for selected epilepsy genes, starting with *SCN1A*. The goal of this activity is to revise the so-called ACMG criteria for *SCN1A*, the criteria by which every diagnostic laboratory interprets variants in the *SCN1A* gene. The current framework is insufficient as it does not pay sufficient attention to the clinical subtleties of *SCN1A*-related disorders and does not include functional data. In order to better understand how functional data can be classified, we have developed a specific dictionary called the Functional Electrophysiological Nomenclature of Ion Channels (FENICS). This dictionary allows for a novel dictionary-based harmonization approach to elucidate patterns in voltage-gated sodium channel variants at the level of individual biophysical properties. We constructed a consensus dictionary of 152 concepts to standardize ion channel functional data and built a harmonized dataset of 5311 annotations across 167 assessments of variants in *SCN1A*, SCN2A, *SCN3A*, and *SCN8A*. The description of functional results beyond gain-of-function versus loss-of-function enabled us to capture the heterogeneity of functional consequences across the epilepsy-associated voltage-gated sodium channel, an aspect of the disease physiology that will likely have implications for therapy development.

The third activity of the Task Force has been the revision of the epilepsy-related Human Phenotype Ontology (HPO), a digital language for epilepsy phenotypes used by many research groups and clinical laboratories, which is completed as of December 2019 and is currently integrated into the full HPO release to be available for the medical genetics and clinical community. We have recently published the revised nomenclature (Lewis-Smith et al., 2021), and we have used this framework to capture the entirety of clinical features for two distinct genetic epilepsies, namely SCN2A-related epilepsies and STXBP1-related epilepsies. This language also allows us to capture how epilepsy phenotypes present over time and how genetic epilepsies respond to anti-seizure medications (Figure 1).

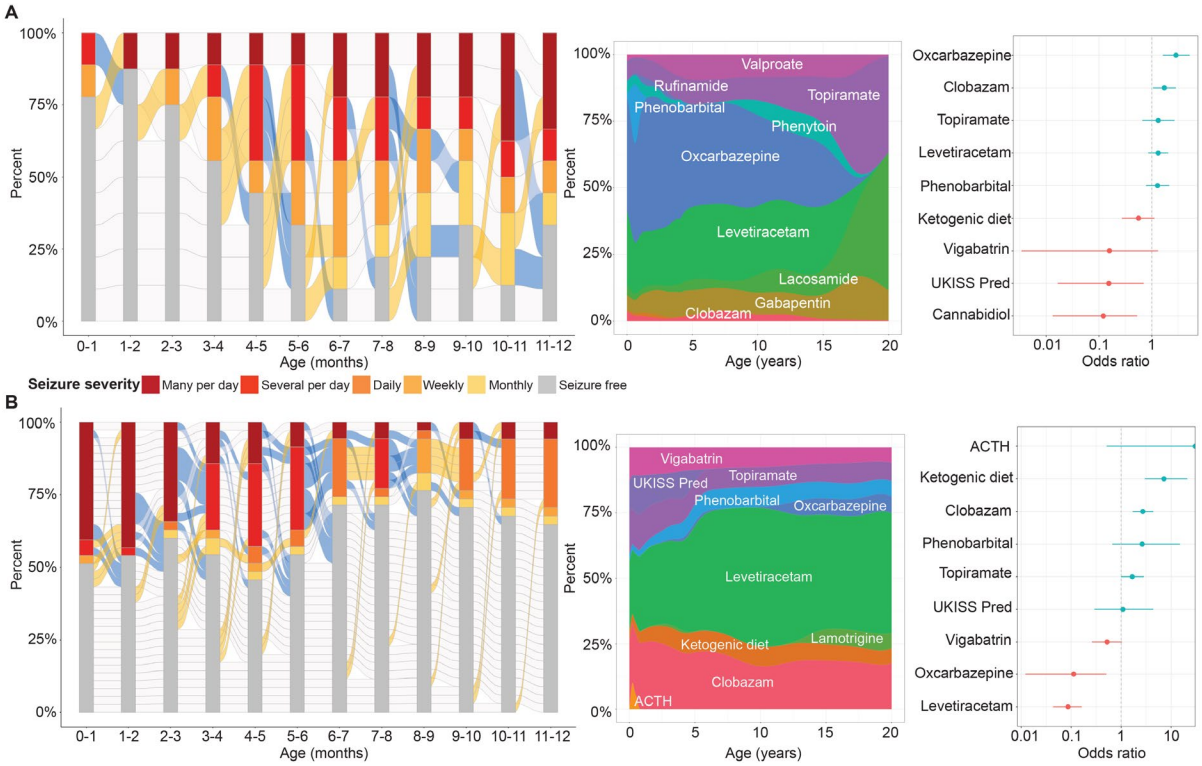

Figure 1. The distribution of seizure frequencies and prescription of various antiseizure treatments with age as well as the odds ratios of achieving a reduction in seizure frequency or maintaining seizure freedom for a selection of medications and the ketogenic diet in patients at our center with (A) *SCN8A*-related and (B) *STXBP1*-related disorders. Seizures tend to become more common over the first year of life among people with *SCN8A*-related disorders, and those taking oxcarbazapine (a sodium channel blocker) are most likely to experience an improvement in seizure frequency. Regarding *STXBP1*, seizures tend to become less common over the first year of life, typically responding well to the ketogenic diet and clobazam. However, those requiring antiseizure medication into adulthood commonly take levetiracetam rather than alternative treatments. Panel b was reproduced and adapted under CC-BY from Xian et al. (2021). Figure derived from Lewis-Smith et al., 2022 (Human Mutation, PMID: 35460582)

ILAE Consortium on Complex Epilepsies

2017 – 2021 Members

Sam Berkovic (Australia), chair
Larry Baum (Hong Kong)
Russ Buono (USA)
Gianpiero Cavalleri (Ireland)
Harkon Harkonarson (USA)
Erin Heinzen (USA)
Michael Johnson (UK)
Reetta Kälviäinen (Finland)
Bobby Koeleman (Netherlands)
Roland Krause (Luxembourg)
Patrick Kwan (Hong Kong / Australia)
Holger Lerche (Germany)
Iscia Lopes-Cendes (Brazil)
Dan Lowenstein (USA)
Terence O'Brien (Australia)
Sanjay Sisodiya (UK)

The main focus of activities of the Consortium in 2021 was the completion of the analysis of "ILAE-3" which is the third analysis of the Consortium increasing the number of subjects with epilepsy to nearly 30,000. This builds on the 2018 *Nature Communications* paper (ILAE-2) with 16,000 subjects. ILAE-3 will be submitted for publication in the first half of 2022. The analyses have shown a large number of new significant hits, particularly for the genetic generalized epilepsies. This appears to be an important discovery upon which others will build. The data were presented by Ciaran Campbell, a PhD candidate in Gianpiero Cavalleri's lab at the AES, December 2021, and this was very well received.

The 2018 ILAE-2 paper, for which the data has become publicly available, has generated a lot of interest both within the epilepsy community where the data is being used to generate polygenic risk scores and in the wider genetics community to look for cross-trait genetic correlations with other disorders, and thus, we believe is perceived as a very valuable neuroscience resource.

The analysis committee for ILAE-3 has been meeting regularly on an approximately monthly basis and is an extremely effective group of analysts devoting a considerable amount of time to the epilepsies. During 2021 a publication dealing with potential drug targets was published based on Consortium data (Mirza N, Stevelink R, Taweel B, Koeleman BPC, Marson AG; International League Against Epilepsy Consortium on Complex Epilepsies*. Using common genetic variants to find drugs for common epilepsies. *Brain Commun*. 2021; 3: fcab287).

Task Force on Sequencing Data Sharing

2017 – 2021 Members

Samuel Berkovic (Australia)
Gianpiero Cavalleri (Ireland)
Ingo Helbig (Germany)
Roland Krause (Luxembourg)

Daniel Lowenstein (USA) Joshua Motelow (USA)
Sanjay Sisodiya (UK)

This Task Force was founded with the goal of bringing together as many sequencing data as possible from patients with genetic epilepsies across the world, and to make them available for the scientific community working on epilepsy genetics. The Task Force has founded the initiative 'ILAE Genomics' with a joint data repository at the Luxembourg Centre for Systems Biomedicine (LCSB), which also hosts the GWAS datasets of the ILAE Consortium of Complex Genetic Epilepsies, the phenotype data of the Epi25 initiative, and GWAS or exome data of major European genetic initiatives (EuroEPINOMICS, EpiPGX). The leading teams in Luxembourg and Tübingen have set up a contractual framework, including ethical and data protection issues, which is currently being finalized with input from the legal departments of all Task Force members and which will be made available in Q2/2022 to the community to broadly join the new consortium. Funding for data storing and processing comes mainly from grants from the two leading teams and some support from the ILAE, which ensures the necessary support for three years.

Meanwhile, large datasets from Epi4K, Epi25 and controls from dbGaP and the UK biobank have been identified and partially downloaded; they are being processed at the LCSB. The goal is to have a first curated dataset with up to 50,000 exomes from individuals with epilepsy and at least the same amount of matched controls by the end of 2022. On a long term, it is planned to fuse the GWAS and exome data initiatives into one consortium, but currently it is not considered useful, since the projects still pursue quite different projects and strategies on common and rare variants, respectively.

Submitted by Holger Lerche