Genetics Commission

Chair
Holger Lerche (Germany)

Members
Daniel Lowenstein (USA), Past-Chair
Piero Perucca (Australia), Secretary
Annapurna Poduri (USA)

Management Committee Liaison
Helen Cross (UK)

Purpose
- To elucidate the genetic architecture of common and rare 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 give recommendations for genetic testing in daily clinical work;
- 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 regular Zoom conferences every two months involving the members of the Genetics Commission and the chairs of the associated Task Forces. In addition, we have held a face-to-face meeting at the 13th European Congress on Epileptology in Vienna (28 August 2018). These meetings have also provided the opportunity to finalize the membership of the different Task Forces (see below), through discussions between the Genetics Commission Chair and members, and the elected Task Force Chairs.

Budget
We have obtained funds for meetings (including a face-to-face meeting at the 2019 International Epilepsy Congress in Bangkok), and for support of the Epilepsiome Project and the new Sequencing Data Sharing initiative.

Planned face-to-face meetings
We will hold a face-to-face meeting at the International Epilepsy Congress in Bangkok on 23 June 2019.

Task Forces

Clinical Genetic Testing in the Epilepsies Task Force
Chair:
Sanjay Sisodiya (UK)

Members:
Hande Caglayan (Turkey)
Katherine 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 Clinical Genetic Testing in the Epilepsies Task Force has been focussing on the current position of various aspects of testing in the epilepsies. The remarkable progress in genetic discovery and understanding has raised new challenges and new opportunities. In particular, there is a need to update guidelines on testing, and to address the increasing need to apply testing in adults with severe epilepsies, often of childhood onset, and to raise awareness of the value of testing in this population. As there are gaps in treatment, it is also clear that there are gaps in availability of clinical genetic testing. The Task Force is seeking to raise awareness and provide information on all these areas. For that purpose, articles to educate and provide guidelines for clinical genetic testing in daily clinical practice will be written for ILAE-related journals *Epilepsia* or *Epileptic Disorders*.

Genetic Literacy Task Force

Co-Chairs:
Nigel Tan (Singapore)
Daniel Lowenstein (USA)

Members:
Samuel Berkovic (Australia)
Peter de Jonghe (Belgium)
Ingo Helbig (Germany)
Jiang Yuwu (China)

Executive Committee Liaison
Helen Cross (UK)

The Task Force moved the Genetics Literacy series from *Epilepsia* to *Epileptic Disorders* in 2018, as part of an overall repositioning of the series by the ILAE leadership. Two articles in the series (Primer part 2, Genetic Generalized Epilepsies) were published in *Epilepsia* in the first half of 2018. The series then moved to *Epileptic Disorders* in the second half of 2018, kicking off with an editorial highlighting the transition, plus a paper on Genetic Epilepsies with Febrile Seizures Plus (GEFS+). Another manuscript on Pharmacogenetics is currently in review with *Epileptic Disorders* and should be published in 2019. The editors of both journals have been very kind in allowing Open Access to the articles in the series, so that the educational purpose of the series can be achieved. We continue to maintain the online MCQ website (sample quiz here) so that readers can check their learning immediately after reading, or refresh their knowledge days/weeks later.

Publications:
Helbig I, Heinzen EL, Mefford HC; International League Against Epilepsy Genetics Commission. Genetic literacy series: Primer part 2-Paradigm shifts in epilepsy genetics. *Epilepsia* 2018;59:1138-1147. doi: 10.1111/epi.14193.

Mullen SA, Berkovic SF; ILAE Genetics Commission. Genetic generalized epilepsies. *Epilepsia* 2018;59:1148-1153. doi: 10.1111/epi.14042.

Tan NC, Berkovic SF, Lowenstein DH. A new home for the Genetic Literacy series. *Epileptic Disord* 2018;20:456. doi: 10.1684/epd.2018.1022.

Myers KA, Scheffer IE, Berkovic SF; ILAE Genetics Commission. Genetic literacy series: genetic epilepsy with febrile seizures plus. *Epileptic Disord*. 2018;20:232-238. doi: 10.1684/epd.2018.0985.

Epilepsiome Task Force

Co-Chairs:
Ingo Helbig (USA)
Heather Mefford (USA)

Members:
Roland Krause (Luxembourg)
Kannan Lakshminarayanan (India)
Nigel Tan (Singapore)
Yi Wang (China)
Ahmad Abou Tayoun (USA)

The Epilepsiome Task Force approached 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 remains the 'Epilepsiome blog', which is the most frequently read resource regarding epilepsy and genes. In 2018, its overall readership increased steadily from 10,000 to 15,000 views per month, with a new post published every week. 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, resulting in the first publication on epilepsy gene curation according to official guidelines (Helbig et al. Hum Mutat 2018). Furthermore, the Task Force took up the task of revising the epilepsy-related Human Phenotype Ontology, a digital language for epilepsy phenotypes used by many research groups and clinical laboratories.

Publication:
Helbig I, Riggs ER, Barry CA, Klein KM, Dyment D, Thaxton C, Sadikovic B, Sands TT, Wagnon JL, Liaquat K, Cilio MR, Mirzaa G, Park K, Axeen E, Butler E, Bardakjian TM, Striano P, Poduri A, Siegert RK, Grant AR, Helbig KL, Mefford HC. The ClinGen Epilepsy Gene Curation Expert Panel-Bridging the divide between clinical domain knowledge and formal gene curation criteria. *Hum Mutat*. 2018;39:1476-1484. doi: 10.1002/humu.23632.

ILAE Consortium on Complex Epilepsies

Chair:
Samuel Berkovic (Australia)

Members:
Larry Baum (Hong Kong)
Russ Buono (USA)
Gianpiero Cavalleri (Ireland)
Hakon 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)
Daniel Lowenstein (USA)
Terence O'Brien (Australia)
Sanjay Sisodiya (UK)

There has been considerable progress over the last 12 months. A major analysis of over 15,000 subjects with epilepsy was completed, largely due to work driven by Remi Stevelink in Bobby Koeleman's lab and Mark McCormack working with Gianpiero Cavalleri. This has resulted in an important paper published in December 2018 in *Nature Communications* which has demonstrated 15 loci for common forms of epilepsy and represents a major advance compared to our initial analysis in 2014. The report received a large amount of publicity and it has generated enthusiasm for even larger studies and the utilization of polygenic risk scores in epilepsy. In 2019 we expect that the sample size will grow to in excess of 25,000 subjects with epilepsy and the 3rd analysis will be done driven largely from the Cleveland Clinic laboratory headed by Dennis Lal.

Publication:
International League Against Epilepsy Consortium on Complex Epilepsies. Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. *Nat Commun* 2018;9:5269. doi: 10.1038/s41467-018-07524-z.

Task Force on Sequencing Data Sharing

Chair:
Holger Lerche (Germany)

Members:
Samuel Berkovic (Australia)
Gianpiero Cavalleri (Ireland)
Ingo Helbig (Germany)
Roland Krause (Luxembourg)
Daniel Lowenstein (USA)
Kevin McKenna (USA)
Sanjay Sisodiya (UK)
Kate E. Stanley (USA)

A new Task Force on Sequencing Data Sharing has been formed with the goal to bring together as many sequencing data as possible from patients with genetic epilepsies across the world. This activity will be similar to the very successful ILAE Consortium on the Genetics of Complex Epilepsies which collected such data for genome-wide association studies. There are already more than 25,000 whole exome sequencing datasets available from large collaborative studies performed in the US, Canada, and in Europe. The TF is currently exploring the possibilities to bring all data together and make them accessible for joint data analysis to the community including appropriate controls. The goal is to have this new platform running in 2020.