Genetics Commission

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Holger Lerche

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Holger Lerche (Germany)

Core Members

Dan Lowenstein (USA), Past Chair
Piero Perucca (Australia), Secretary
Annapurna Poduri (USA)

Management Committee Liaison

J. Helen Cross (UK)

Purpose

- To elucidate the genetic architecture of complex 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 four Zoom meetings involving the members of the Genetics Commission and the chairs of the associated Task Forces (March 16th, July 2nd, October 7th and December 21st). These meetings have provided the opportunity to coordinate the activities of the different Task Forces (see below), through discussions between the Genetics Commission and the elected Task Force Chairs.

Budget

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

Task Forces

Clinical Genetic Testing Task Force (initiated together with the ILAE Diagnostics Commission)

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 Clinical Genetic Testing in the Epilepsies Task Force has continued to focus 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 currently working on three separate manuscripts, seeking to raise awareness and provide information on all these knowledge gaps. The most advanced is being led by Yvonne Weber, as a joint effort from the Commission and the Clinical Genetic Testing Task Force which will be submitted within Q1 2021. The other two manuscripts are less advanced, but will hopefully be completed by Q2 2021.

Genetic Literacy Task Force

Members

Nigel Tan (Singapore), **co-chair**
Dan Lowenstein (USA), **co-chair**
Sam Berkovic (Australia)
Peter de Jonghe (Belgium)
Ingo Helbig (Germany)
Jiang Yuwu (China)

Helen Cross (UK), **Management Committee Liaison**

The Task Force's work continued despite the ongoing COVID-19 pandemic. The next paper in the series on familial focal epilepsies has been reviewed by the Task Force and the Commission; it awaits final clearance by the ILAE Publication Committee before submission to *Epileptic Disorders*. We are planning the subsequent paper on Genetic Counselling.

We continue to maintain the online MCQ website (sample quiz here) so that readers can do self-learning immediately after reading, or days/weeks later to refresh their knowledge.

Epilepsiome Task Force

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)

Junior members (curating ILAE classification within the Human Phenotype Ontology):

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

Helen Cross (UK), **Management Committee Liaison**

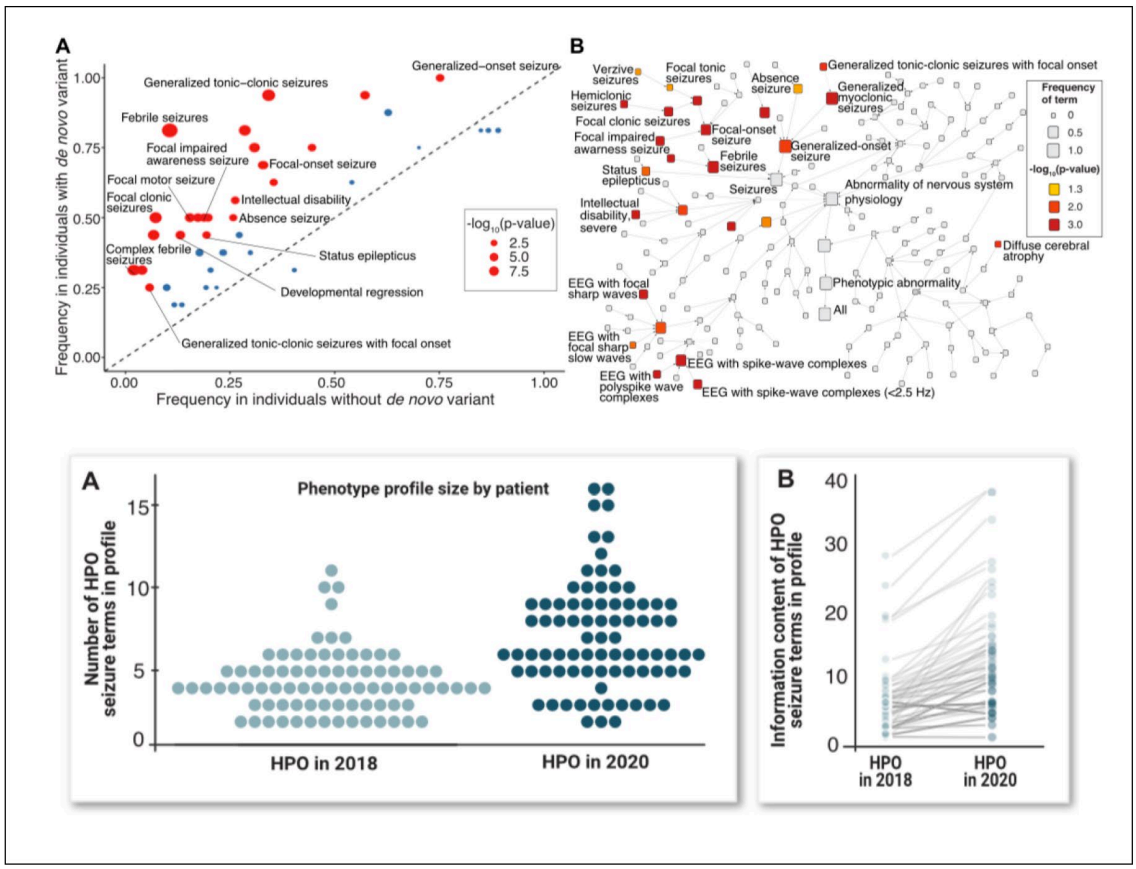

Figure 1 *(adapted from Figures 3, 4 by Koehler et al., 2021). Upper panel: HPO-based analyses demonstrate the clinical features associated with diagnostic variants in SCN1A in published cohorts with developmental and epileptic encephalopathies of various known, or unknown but presumed genetic, etiologies. Fisher's exact test p-value for each term indicates the significance of the association between the HPO term and the presence of a diagnostic SCN1A variant in the cohort. (A) The frequency of HPO terms in SCN1A variant carriers versus non-carriers regardless of age. (B) The same data presented to demonstrate the conceptual relationships between associated features within the structure of the HPO. (A) and (B) modified from (24) with only a selection of terms labeled for legibility. Lower panel: (A) The number of seizure terms applicable to the same clinical data from 82 individuals, and (B) the total information content of seizure terms of the same individuals according to the new and previous HPO seizure subontologies, where the information content of each term is equal to the negative logarithm of the proportion of individuals annotated with the term (Lewis-Smith et al., manuscript in preparation).*

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' (http://epilepsygenetics.net/), which remains the most frequently read resource for epilepsy and genes with up to 10,000 unique visitors per month. During the last period, we finalized the revision of the HPO terminology, which is currently submitted for publication (Lewis-Smith et al., submitted). In addition,

the HPO revision in the epilepsies was featured in the most recent HPO summary publication (Koehler et al., 2021, Figure 1)

Publications:

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.

Köhler S, Gargano M, Matentzoglu N, Carmody LC, Lewis-Smith D, Vasilevsky NA, Danis D, Balagura G, Baynam G, Brower AM, Callahan TJ, Chute CG, Est JL, Galer PD, Ganesan S, Griese M, Haimel M, Pazmandi J, Hanauer M, Harris NL, Hartnett MJ, Hastreiter M, Hauck F, He Y, Jeske T, Kearney H, Kindle G, Klein C, Knoflach K, Krause R, Lagorce D, McMurry JA, Miller JA, Munoz-Torres MC, Peters RL, Rapp CK, Rath AM, Rind SA, Rosenberg AZ, Segal MM, Seidel MG, Smedley D, Talmy T, Thomas Y, Wiafe SA, Xian J, Yüksel Z, Helbig I, Mungall CJ, Haendel MA, Robinson PN. **The Human Phenotype Ontology in 2021**. Nucleic Acids Res. 2021 Jan 8;49(D1):D1207-D1217. doi: 10.1093/nar/gkaa1043.

ILAE Consortium on Complex Epilepsies

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)

Following a turnover in voluntary personnel (data analysists), the activities of the Consortium are progressing well. In particular, the third analysis (ILAE-III) is progressing with inclusion of a large number of new samples from the Epi25 Collaborative. An inherent technical issue is merging data from different cohorts where genotyping was done on different platforms but this now appears largely solved. Cooperation between the Consortium and the Broad Institute who generated the new data has been excellent. The new analysis is expected by mid-2021.

Considering the increasing interest in Polygenic Risk Scores, the ILAE Consortium Complex Epilepsies datasets have received much attention and interest from research groups within and outside of epilepsy.

Publications: nil in 2020.

Task Force on Sequencing Data Sharing

Members:

Samuel Berkovic (Australia)
Gianpiero Cavalleri (Ireland)
Ingo Helbig (Germany)
Roland Krause (Luxembourg)
Daniel Lowenstein (USA)
Sanjay Sisodiya (UK)
Joshua Motelow (USA)

The newest of the Task Forces under the Genetics Commission, the Task Force on Sequencing Data Sharing, was founded with the goal of bringing together as many sequencing data (mainly exomes) 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 established a joint data repository in Luxembourg. Some datasets from previous European studies are already in place, available datasets are currently being downloaded and processed together with available controls, mainly from dbGaP, but also from other sites, such as the UK Biobank. Groups working on epilepsy genetics having additional own data have been approached worldwide by e-mail and in two video conferences, as well as patient organizations and potential industrial partners. A consortium contract, data access and data sharing agreements have been prepared and will be available very soon for all interested partners.

Submitted by Holge Lerche