Genetics Commission

Annual Report 2023

MEMBERS

Piero Perucca (Australia), chair
Holger Lerche (Germany), past chair
Alina Esterhuizen (South Africa)
Iscia Tereznha Lopes Cendes (Brazil)
Meng Han Tsai (Taiwan)
J. Helen Cross (UK), MC liaison

HIGHLIGHTS

- The publication of the third genome-wide association study (ILAE 3) by the ILAE Consortium on Complex Epilepsies in the prestigious *Nature Genetics*. This analysis - the largest of its kind, comprising almost 30,000 cases with epilepsy and over 50,000 controls - has substantially advanced our understanding of the genetic architecture of the common epilepsies, identifying 26 genome-wide significant loci, 19 of which specific to genetic generalized epilepsy. This analysis is also a remarkable example of highly successful international collaborations, having brought together over 150 researchers across Europe, Australia, Asia, South America, and North America.
- Three new publications of the ILAE Genetic Literacy Series. The first is focused on 'self-limited familial epilepsy syndromes with onset in neonatal age and infancy', led by Charissa Millevert and Sarah Weckhuysen (*Epileptic Disord* 2023;25:445-453). The second discusses 'postmortem genetic testing in sudden unexpected death in epilepsy', led by Richard Bagnall and Piero Perucca (*Epileptic Disord* 2023;25:472-479). The third is on 'progressive myoclonus epilepsies', led by Jillian Cameron, Colin Ellis, and Sam Berkovic (*Epileptic* Disord 2023;25:670-680).
- The recent completion of the survey on genetic testing practices around the world by the Task Force on Clinical Genetic Testing in the Epilepsies. The survey, launched in May 2023, has received 1,759 responses, which is the strongest response ever received by an ILAE survey.

ACTIVITIES

The Genetics Commission has carried out several activities through its associated Task Forces.

<u>Genetic Literacy Task Force</u>

Daniel H. Lowenstein (USA), co-chair
Nigel Tan (Singapore), co-chair
Norman Delanty (Ireland)
Alina Esterhuizen (South Africa)
Faiza Fakhfakh (Tunisia)
Ingo Helbig (Germany)
Amy McTague (UK)
Emma Palmer (Australia)

The Task Force has continued to organise the Genetic Literacy Series in line with the education mission of the ILAE, with contributions from all over the world. Three articles have been published in *Epileptic Disorders* in 2023, and five more are in preparation.

Epilepsiome Task Force

Ingo Helbig (USA), co-chair
Heather Mefford (USA), co-chair
Ahmad Abou Tayoun (USA)
Ganna Balagura (Italy)
Gordon Jing (China)
Lakshminarayanan Kannan (India)
Roland Krause (Luxembourg)
David Lewis-Smith (USA)
Nigel Tan (Singapore)

The Task Force has maintained the Epilepsiome blog, which remains a widely accessed resource on epilepsy genetics. In collaboration with ClinGen, members of the Task Force have contributed to the development of classification rules for the interpretation of variants in sodium channel genes.

Task Force on Sequencing Data Sharing (ILAE Genomics)

Holger Lerche (Germany), chair
Samuel F. Berkovic (Australia)
Roland Krause (Luxembourg)
Daniel H. Lowenstein (USA)
Gianpiero Cavalleri (Ireland)
Ingo Helbig (Germany)
Sanjay Sisodiya (UK)

The Task Force has worked with different groups to assemble a large set of sequenced data. Almost 6000 epilepsy cases and over 13,000 control exomes have been collected from different sources, including CoGIE, EpiPGX, Epi25, Epi4, CENet, EMA and UKNN. A greater number of cases and controls are being sought.

Task Force on Clinical Genetic Testing in the Epilepsies

Andreas Brunklaus (UK), co-chair
Gaetan Lesca (France), co-chair
Alina Esterhuizen (South Africa)
Katherine Helbig (USA)
Michael Hildebrand (Australia)
Rebecca Macintosh (Australia)
Gagandeep Singh (India)
Iscia Tereznha Lopes Cendes (Brazil)
Chahnez Charfi Triki (Tunisia)
Sarah Weckhuysen (USA)

The Task Force launched a survey in May 2023 to assess genetic testing practices around the world. This was closed before the end of 2023. Through coordinated efforts, including great support from the ILAE, the survey has received a total of 1,759 responses with wide geographic distribution. The data is now being analyzed.

ILAE Consortium on Complex Epilepsies

Chair: Sam Berkovic (Australia)

The Consortium has had a successful year with the publication of its third GWAS analysis (ILAE 3) in Nature Genetics. Planning of the fourth GWAS of the Consortium is under way, with the goal of increasing substantially the number of epilepsy cases across different ethnical backgrounds.

ACCOMPLISHMENTS

A major accomplishment has been the publication of the third GWAS analysis (ILAE 3) by the ILAE Consortium on Complex Epilepsies in the prestigious *Nature Genetics* journal. By uncovering 26 genome-wide significant loci, 19 of which specific to genetic generalized epilepsy (GGE), this analysis has substantially furthered our understanding of the genetic architecture of common epilepsies, particularly the GGEs. The summary statistics of ILAE 3 are now fully accessible and are being used by different groups worldwide.

Another important accomplishment has been completion of the survey to assess genetic practices around the world by the Task Force on Task Force on Clinical Genetic Testing in the Epilepsies, which yielded 1,759 responses. This is strongest response ever to an ILAE survey.

A third noteworthy accomplishment has been the development of classification rules for the interpretation of variants in voltage-gated sodium channel genes, led by the Chairs of Epilepsiome Task Force in work done with ClinGen.

RESEARCH & ARTICLES PUBLISHED

1. International League Against Epilepsy Consortium on Complex Epilepsies. GWAS meta-analysis of over 29,000 people with epilepsy identifies 26 risk loci and subtype-specific genetic architecture. *Nat Genet* 2023;55(9):1471-1482.

2. Stevelink R, Koeleman BPC, Sisodiya SM; International League Against Epilepsy Consortium on Complex Epilepsies. Distinct genetic basis of common epilepsies and structural magnetic resonance imaging measures. *Epilepsia* 2023;64:e82-e86.

3. Cameron JM, Ellis CA, Berkovic SF; ILAE Genetics Commission; ILAE Genetic Literacy Task Force. ILAE Genetics Literacy series: Progressive myoclonus epilepsies. *Epileptic Disord* 2023;25:670-680.

4. Bagnall RD, Perucca P; ILAE Genetics Commission. ILAE Genetic Literacy Series: Postmortem Genetic Testing in Sudden Unexpected Death in Epilepsy. *Epileptic Disord* 2023;25(4):472-479.

5. Millevert C, Weckhuysen S; ILAE Genetics Commission. ILAE Genetic Literacy Series: Self-limited familial epilepsy syndromes with onset in neonatal age and infancy. *Epileptic Disord* 2023;25(4):445-453.

MEETINGS

In 2023, we had three Zoom meetings (30 March, 20 June, and 20 December) and one 'hybrid' meeting (1 September 2023 in Dublin, Ireland) involving Members of the Genetics Commission and chairs of the associated Task Forces. These meetings have provided the opportunity to plan and coordinate the activities of the different Task Forces through discussions between the Genetics Commission Members and the Task Force Chairs.

Report submitted by Piero Perucca