

COMMISSION ON GENETICS



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Aims

- To organize the search for human epilepsy genes on a worldwide scale through broad participation by members of ILAE chapters.
- To prioritize complex epilepsies suitable for multicenter collaborative gene mapping studies.
- To make the results of genetic research on the epilepsies readily accessible to clinicians.
- To improve the public understanding of genetic factors in epilepsy.
- To work with related ILAE commissions to increase understanding of newly identified genes and their role in basic mechanisms of epileptogenesis and anti-epileptogenesis.
- Improving knowledge and application of genetics in epilepsy across the world.

Commission Activities

June 2014 through June 2015

Initiative 1: Facilitate access to information regarding the identification and interpretation of gene mutations associated with epilepsy.

- a. EpiGAD: The EpiGAD has been regularly maintained, updated and audited, and is up-to-date for 2015. There continues to be ongoing access to the database, which is encouraging as it shows the epilepsy community at large finds the information there helpful. To unify the Commission on Genetics approach to online epilepsy genetics initiatives, we plan to merge epiGAD into the Epilepsioime project in the next 12-18 months.
- b. ILAE Genetics Commission Blog: To provide better outreach and communication to the professional community, the ILAE Commission

on Genetics has decided to maintain a blog on topics related to genes and seizures. We have adopted the "Beyond the Ion Channel" blog that was previously initiated by the European EuroEPINOMICS consortium. As of June 2014, this blog is now officially run by the ILAE Commission on Genetics and we have usually posted 1-2 posts per week that are well received by the professional community. We have completed our move to a self-hosted website and have rebuilt our audience and online presence of the new website, even increasing our readership by more than 50% over the last few months. Currently, the ILAE Genetics blog receives 5,000-7,500 views per months, largely from the US and Europe, but with readers from more than 40 countries worldwide. Looking back at the last 18 months of our blog as the information portal of the ILAE, Commission on Genetics, our blog has had more than 60,000 visitors including epilepsy professionals, patient organizations and families. In addition to the blog, we issue "The Channelopathist," a weekly email newsletter for the epilepsy community. For the commission, the blog has proven extremely valuable as an outreach tool the community.

- c. Epilepsioime: As an extension of our current online strategy, we have developed a concept for a comprehensive database on epilepsy and genes that would allow professionals, patient organizations and families to quickly gather relevant information on epilepsy-related genes. Over the last 12 months, we have had various strategic discussions regarding the particular niche and relative role of the Epilepsioime project compared to other available online resources (ClinGen, GeneReviews). The Epilepsioime will integrate with these other resources but will have "trusted expert opinion" and regular updates as distinguishing features. We have enlisted the help of 40 scientific volunteers who are organized in expert groups on specific genes and who are fully engaged in the gene curation efforts of this project. The Epilepsioime project is currently in a beta phase where we have reviewed and published first gene summaries on 15 genes and are currently fine-tuning the Epilepsioime format and the process of updating information. With respect to the overall format, we are coordinating efforts with other initiatives such as ClinGen, ClinVar and EGI and are planning to provide first proposal for a new visually oriented web interface prior to presenting a full project

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proposal for the ILAE to approve. We are also exploring different options of supporting this project through patient organizations such as CURE (Citizens United for Research in Epilepsy) and intramural grants of the participating institutions.

Initiative 2: Assist in the creation of a centralized database of complete sequence data with variant

Calls paired with clinical information for as many patients as possible throughout the world that are sequenced for epilepsy of unknown cause. This concept, formally known as the “Epilepsy Genetics Initiative” (EGI) has now been launched as a result of planning between the NIH-sponsored “Epi4K Center Without Walls” and the Chicago-based “Citizens United for Research in Epilepsy,” and with substantial assistance from members of the Commission on Genetics. See: <http://www.cureepilepsy.org/egi/index.asp>. ILAE members are encouraged to track the growth of this project and become actively involved in helping patients learn about the benefits of participation.

Initiative 3. Continue the important work of the ILAE Consortium on Complex Epilepsies, led by Sam Berkovic

The highlight of the consortium’s work this year was the publication in *Lancet Neurology* (Sept 2014; <http://www.ncbi.nlm.nih.gov/pubmed/?term=lancet+neurology+++consortium+on+complex+epilepsies>) of our first meta-analysis of GWAS data involving nearly 9,000 subjects. This demonstrated risk alleles for the combined epilepsy cohort and for genetic generalized epilepsy. The consortium is now undertaking subanalyses of more specific phenotypes and of the relationship of loci influencing brain structure to those raising risk for epilepsies. Further collaborations are being planned to investigate epilepsy comorbidities, by combined analyses with consortia investigating migraine and neuropsychiatric disorders. Finally, the possibility of enlarging the data set of epilepsy patients is being explored.

Initiative 4: Improve genetic literacy among both patients and providers

- a. Educational Brochures: An English version of the educational brochure entitled “Epilepsy and Genetics: Things You Want to Know,” designed by Alica Goldman and other commission

members for patients and family members, is now available through the ILAE Commission on Genetics website. Positive public reception of the material has prompted culturally sensitive Spanish and Arabic translations aimed at the Spanish speaking Latin American and Arabic populations (<http://www.ilae.org/Commission/genetics/>). These documents are now posted on the ILAE website. Broad public interest in learning the essential principles of epilepsy genetics has led to Japanese translation that is under the review of the Japanese Epilepsy Society and the approval is planned for early 2016. At the same time, the commission plans to pursue the same strategy for creating similar brochures in Chinese and other languages considered to be high priority by the ILAE.

- b. Genetic Literacy Series: Recognizing that clinicians are often uncertain about or uncomfortable with genetic testing in epilepsy and epilepsy genetics, the Commission on Genetics, under the leadership of Nigel Tan, is starting a new series on genetic literacy in *Epilepsia*. This series of 12 papers aims to update and educate practicing clinicians about clinically relevant epilepsy genetics, using modern evidence-based educational methods to promote learning and knowledge retention. The first paper in this series has just been published in November 2015, with the second paper currently under review after revisions, and the 3rd to 5th papers being in the writing phase. We are encouraged by the reviewers’ feedback and comments, and we anticipate this series will run through 2016 to mid-2017.

Recommendations for Future Work

We feel that there needs to be further effort placed on helping clinicians stay up-to-date on the latest findings in epilepsy genetics, given that we are now beginning to see the emergence of individualized therapies based on the patient’s genomic profile. We also need to encourage patients and family members living with epilepsy to understand the role that genetic testing may play in the evaluation of a seizure disorder, and the value of involvement in the Epilepsy Genetics Initiative. Finally, we intend to explore the potential value of a global registry of patients with defined epilepsy gene mutations, with the goal of expediting observational studies and treatment trials.