EUROCORES Programme
European Collaborative Research

Functional Genomic Variation in the Epilepsies (EuroEPINOMICS)

Review Panel Final Consensus Statement

Background

The objectives of EuroEPINOMICS were to identify novel epilepsy genes and genetic variants predisposing to epilepsy and drug response, and to unravel molecular pathways. The aim of EuroEPINOMICS was to apply innovative molecular genetic techniques in large European cohorts of well-characterized epilepsy patients by combining the resources of former European collaborative projects. Pharmacogenetics was also included in the objectives in order to identify possible genetic risk factors affecting drug response, side effects, refractoriness and teratogenicity. Functional studies using state-of-the-art techniques were used to elucidate the epileptogenic mechanisms of the identified genetic variants.

There were four Collaborative Research Projects (CRPs) involved in EuroEPINOMICS:

- Genetics of Rare Epilepsy Syndromes (RES)
- Genetic Targets of Epileptogenesis and Pharmacoresistance in Brain Glial Cells (Epiglia)
- Epigenetic Pathomechanisms Promoting Epileptogenesis in Focal and Generalised Epilepsies (EpiGENet)
- Complex Genetics of Idiopathic Epilepsies (CoGIE)

The total research budget was of **6.74 million €** (managed by the national funding organisations) while the total networking and dissemination budget was of **281,231€** (managed by the ESF).

Thirteen funding organizations and countries financially supported the EuroEPINOMICS projects. See: http://www.esf.org/coordinating-research/eurocores/running-programmes/euroepinomics/governing-bodies/management-committee.html

ESF website: www.esf.org/euroepinomics and www.euroepinomics.org

Evaluation of the EuroEPINOMICS Programme by the Review Panel

The four Project Leaders' reports were made available to the 12 Review Panel members. Eight of them performed the assessment remotely and the remote evaluation was completed by a teleconference attended by 4 Review Panel members on Thursday 20 November 2014. The draft consensus statement was then circulated among all Panel members in order to obtain final approval.

Progress in the Collaborative Research Projects (CRPs)

The panel noted a very good overall performance of the programme, with very good achievements, often beyond the initial goals. Excellent publications in highly ranked journals (*Nature Genetics, PNAS*) represent a major scientific output (note: at least one

more article submitted by RES and CoGIE, a Letter in *Nature Genetics*, has been recently accepted for publication). The panel members who attended the final conference in Tuusla (FI) on 23-25 April 2014 (report) noted that the Principal Investigators (PIs) not only focused on reporting highlights or exchanging novel information, but also on discussing possible collaborations for future projects and applications for future funding.

Scientific highlights of the 4 CRPs can be summarised as follows:

1. **EuroEPINOMICS** led to the first genome-wide association study (GWAS) in IGE which revealed significant association signals at 1q43, 2p16.1, 2q22.3 and 17q21.32. EuroEPINOMICS also contributed to a world-wide collaboration (International League Against Epilepsy – ILAE - consortium on genetics of complex epilepsies) including >8,500 people with epilepsy and >26,000 controls to describe the first two loci with genome-wide significance across all epilepsy syndromes (at 2q24.3, implicating SCN1A, and at 4p15.1, harbouring the protocadherin gene PCDH7 not previously implicated in epilepsy).

2. **CoGIE** aimed to further elucidate the complex genetics of the two most common groups of inherited epilepsies – idiopathic generalised epilepsy (IGE) and idiopathic focal epilepsy with rolandic spikes (RE), and to determine the overlaps and boundaries to rare and more severe forms of idiopathic/genetic/non-lesional epilepsies (epileptic encephalopathies = EE) in close collaboration with the **RES** CRP. This resulted in whole exome sequencing of 1-2 affected individuals of 243 independent families and whole genome sequencing of 15 whole families concerning IGE. In addition, CoGIE researchers sequenced the exomes of affected individuals of 250 families with RE and associated phenotypes, and whole genomes of all individuals in 5 families.

   The first breakthrough in the etiology of common complex genetic epilepsy syndromes was achieved in a large cross-CRP collaboration, e.g. identification of mutations and microdeletions in GRIN2A encoding the NR2A NMDA receptor subunit, as a major risk factor of different subtypes of RE, with clear genotype-phenotype relationships; the detection of mutations in STX1B in fever-associated epilepsy syndromes; the detection of a frequent recurring mutation in progressive myoclonus epilepsy, clinically very similar to the Unverricht-Lundborg type.

   In addition in terms of clinical practice, **RES and CoGIE** published the first next generation sequencing approach for diagnostic purposes in the epilepsies. A panel of >300 genes associated with epilepsy was sequenced in parallel, in this first approach in 33 patients with suspected but unclear genetic causes of epilepsy. This has led to the evaluation of data of >1,000 diagnostic panels of people with epilepsy from Europe.

3. **RES** was dedicated to the delineation of the genetic basis of severe childhood epilepsies and epileptic encephalopathies (EEs). RES contributed in several ways to the overall programme. Within RES, whole exomes/genomes of patients with severe epileptic syndromes were sequenced. A platform was developed to share variants and mutations found in these cohorts with the other CRPs, mainly with the CoGIE-CRP that looks at the genetics of common epilepsy syndromes.

4. **EpiGENet** has uncovered the depth of epigenomic complexity in epilepsy, and contributed to the design of two successful EU Framework Programme 7 projects entitled EPITARGET and DESIRE. These FP7 consortia have their central idea in the concept of combinatorial approaches to the treatment of epilepsy, recognising the complexity that EpiGENet was central to revealing.

5. **Epiglia** established new animal models in Oslo and Utrecht: 1) the intracortical kainate injection model in mice and 2) the febrile seizure mouse model (hyperthermia induced by warm air), established at Bonn University. Epiglia was found disappointing compared to the other 3 CRPs in terms of research outputs but the panel acknowledges that this CRP started 1 year later due to funding issues. However, the teams of this CRP are now well-organised and will undoubtedly generate important results in the near future.

While basic research findings are impressive, translational aspects and the transition from bench to bedside leading to potential new therapies have been very limited but this may have been a too ambitious goal for just 3 years. There is no doubt that excellent results and more very good papers will follow.

Programme integration

The programme helped foster collaborative research in Europe in the field of rare and common epilepsies. It was the very first time that so many European centers united and worked together with a highly impressive level of collaboration, even though the expansion of the programme was geographically restricted due to the lack of funding from several European countries.

Numerous meetings, workshops, training courses, travel grants, short visits were funded during the course of the programme and ended with a final conference in April 2014 to which all 4 CRPs contributed.

A major asset of EuroEPINOMICS lies in its team of young, open-minded, enthusiastic investigators.

Three CRPs contributed effectively to integration within the whole programme by sharing samples, databases, genotypic and phenotypic information (RES, CoGIE, EpiGENet), thus leading to joint publications of high quality (especially RES and CoGIE). However, Epiglia did not demonstrate integration with other CRPs within the programme, despite this being strongly encouraged from programme initiation and at the mid-term review. The EpiGlia focus on animal models certainly provided opportunities for sharing expertise in the use of such epilepsy models with other CRPs. While Epiglia PIs may not have had data to share with PIs from the other CRPs, a greater focus on how to bring therapeutics from animal models to humans could have contributed usefully to the translational aspects that are somewhat lacking in this programme.

Networking, training and dissemination

Training of the young generation through training courses, short visits and dissemination travel grants, and encouraging mobility across CRPs, is a commendable highlight of EuroEPINOMICS. Again, RES and CoGIE largely benefitted from these activities, and Epiglia could have participated more by favouring the training of young pre-clinical researchers.

The blog on epilepsy genetics (now available from epilepsygenetics.net) run by Roland Krause (CoGIE-IP5) and Ingo Helbig (RES-IP2) has been developed to represent now THE information platform in the field which is read worldwide and has been taken over recently by the ILAE. The media coverage of the programme was also very good and there was a successful social media communication plan.

Besides the blog, the RES project formed a VARBANK platform with rare sequencing data, and a web-based platform BENCH. All these were shared with the CoGIE group and represented an added value to the programme. EpiGENet established a database of promotor methylation of the human epileptic hippocampi.

On a negative note, the panel noted the lack of interaction with patient organisations.

General comments and other feedback

In summary, the programme has achieved its main goal by fostering collaborative research in epilepsy in Europe with a focus on basic research on genetics and pathophysiology of rare and common epileptic syndromes. Synergies were created across teams and CRPs, so that the critical mass required for the study of epilepsies was reached. The scientific output is also remarkable with many high-profile publications, although uneven among the individual CRPs and across CRPs.

Given the focus on basic genetic research and disease mechanisms and the complexity of the disorder, the main translational objectives achieved by the programme are somewhat limited which is disappointing. The EuroEPINOMICS findings should have an impact on clinical practice in a way that improves the lives of people with epilepsy. However, specific findings can be of significant benefit for a few families with rare disorders through improved diagnosis and genetic counseling.

In conclusion, the panel recommends the following:

- Apply for funding in order to gain clinical impact, i.e. pharmacological applications (new therapies) and/or biomarkers of pharmacoresistance to anti-epileptic drugs
- Maintain the skills and high training level of the young generation
- Analyse the vast amount of data that was generated during the programme duration
- Make publicly available the webpages (to be updated) as well as the genotype and phenotype data (databases, biobanks)
- Continue the dissemination to the research community via the blog, now taken up by ILAE
- Implement a dissemination plan with patient organisations

Two additional activities will take place until April 2015 with the unspent networking and dissemination funds:

1. Training Programme & Specialised Course: recruitment of familial epilepsies in Israel/Palestine, 23 April - 31 December 2014 (convenor: Ingo Helbig, University Medical Center Schleswig-Holstein, Kiel, DE, and Children's Hospital of Philadelphia, USA - RES)
2. Symposia on Epigenetic mechanisms in epileptogenesis (Sölden, AT), 6-11 April 2015 (convenor: Günther Sperk, Medical University Innsbruck, AT - EpiGENet)

The panel hopes the established collaborations will continue and expand in order to keep the momentum.