

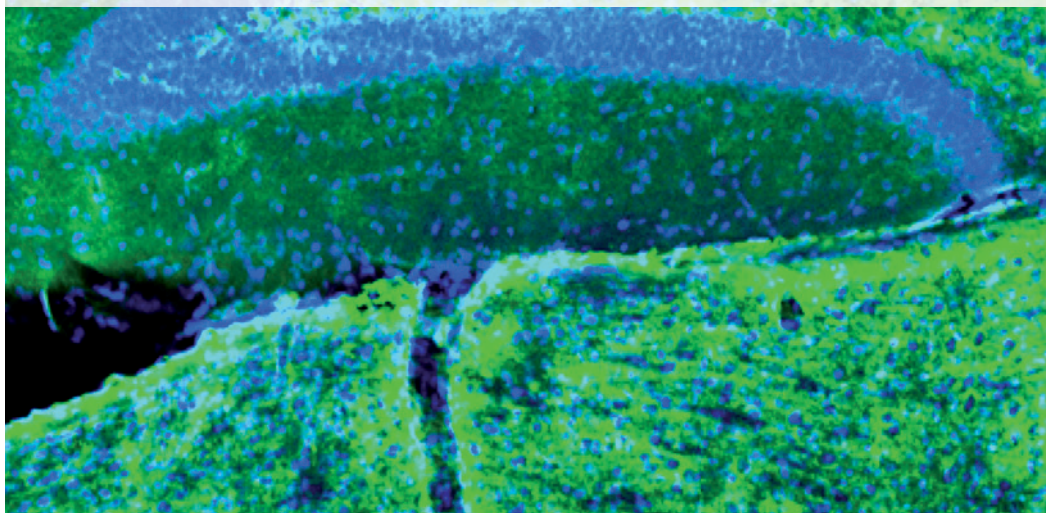


EUROPEAN  
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**EUROCORES Programme**

# **EuroEPINOMICS**

**Functional Genomic Variation in the Epilepsies**



# EUROCORES Programme

European Collaborative Research

Epilepsy is a common serious neurological disorder affecting ~6 million people in Europe. Despite the many new drugs released in the last 20 years, one third of all epileptic patients remain refractory to pharmacotherapy implying the need to develop novel treatments with innovative mechanisms of action. The discovery of the first epilepsy genes has identified novel molecular pathways involved in epileptogenesis and helped to define new drug targets. These findings have come mostly from rare monogenic forms of epilepsy, whereas the complex genetics of the common epilepsy syndromes and the genetic factors determining a patient's response to antiepileptic drugs (pharmacogenetics) are largely unknown.

## **The objectives of EuroEPINOMICS are:**

1. to identify novel epilepsy genes and genetic variants predisposing to epilepsy and drug response, and
2. to unravel their molecular pathways.

EuroEPINOMICS aims to bring together scientific expertise and resources of leading European research groups in order to:

1. provide high-resolution maps of genetic risk factors for common epilepsy syndromes,
2. dissect genetic determinants of the response to antiepileptic drugs, and
3. elucidate the mechanisms of epileptogenesis.

## **The long-term scientific goals are:**

1. the identification of novel therapeutic targets, and
2. an individualised pharmacotherapy.

EuroEPINOMICS will apply innovative molecular genetic techniques in large European cohorts of well-characterised epilepsy patients (N>8000) by combining the resources of various European collaborative projects (EPICURE, EPIGEN, EURIPIDES, EURAP).

## **The molecular genetic studies will focus on:**

1. common idiopathic epilepsy syndromes,
2. mesial temporal lobe epilepsy,
3. febrile seizures, and
4. rare monogenic epilepsy syndromes.

Pharmacogenetic studies are expected to identify genetic risk factors affecting drug response, side effects, refractoriness and teratogenicity. Complementarily, comprehensive functional studies using state-of-the-art techniques will elucidate the epileptogenic mechanisms of the identified genetic variants.

# Collaborative Research Projects (CRPs)

## Genetics of Rare Epilepsy Syndromes (RES)

(CNCS, DFG, ETF, FWO, MICINN\*, MNiSW, RCN, SNF, TÜBITAK)

\* Support not confirmed at the time of printing

This CRP aims to decipher the genetic basis of many rare epilepsy syndromes (RES) by bringing together the expertise of epileptologists with access to large patient cohorts and molecular genetic teams with a vast experience in locus and gene identification.

Collectively, this team of researchers will recruit the largest cohort of patients with RES to date and, for the first time, collect comprehensive clinical, electrophysiological and genealogical data in a standardised way. Novel genes for seizure disorders will be identified using a broad range of technologies including large-scale copy number variation (CNV) analysis and next-generation sequencing techniques. These technologies will be applied in a systematic genetic workflow to streamline analysis efficiency. Finally, genotype-phenotype correlation will be performed to identify novel disease entities based on genetic findings.

### Project Leader:

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## **Genetic Targets of Epileptogenesis and Pharmacoresistance in Brain Glial Cells (Epiglia)**

(AKA, DFG, RCN)

Temporal lobe epilepsy (TLE) consists of several subgroups of which Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS) is the most severe one. There is also a high association between TLE and febrile seizures. Identifying the different TLE subgroups may open new possibilities to tailor pharmacological treatment. Recent findings suggest that modified glial function may play an important role in the hyperexcitability of neuronal tissue promoting epileptogenesis and disease progression, specifically in TLE.

This project tests the hypothesis that astrocytes play a critical role in the generation, spreading and maintenance of seizures in different TLE subgroups. For that purpose, we aim to focus on genetic studies on glia targets, functional studies in living human epileptic tissue and MTLE-HS mouse models including febrile seizures, studies on knockout animals, and other functional and molecular biological studies.

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## **Epigenetic Pathomechanisms Promoting Epileptogenesis in Focal and Generalised Epilepsies (EpiGENet)**

(AKA, DFG, FWF, MNiSW)

About 1% of the population has epilepsy, and 30% of the patients lack response to currently available antiepileptic drugs. The onset and progression of drug-resistant seizures remain, however, difficult to predict in affected patients, irrespective of their epileptogenic condition. The objective of this CRP is to characterise common epigenetic pathomechanisms of epileptogenesis. Epigenetic mechanisms are self-perpetuating, post-translational modifications of nuclear proteins and DNA that can produce lasting alterations in chromatin structure and gene expression patterns. Results will be obtained from animal models and human brain specimens using advanced experimental tools, and will help to identify novel targets for pharmacotherapy in these difficult-to-treat patients.

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## **Complex Genetics of Idiopathic Epilepsies (CoGIE)**

(AKA, DFG, FNR, FWF, OTKA)

Idiopathic Generalised Epilepsy (IGE) and Rolandic Epilepsy (RE)/Centro-Temporal Spikes (CTS), the two most common idiopathic epilepsy syndromes, represent prototypes for common diseases with complex inheritance. Rare mutations (mainly in ion channels) and different microdeletions (in up to 3% of IGE) have been identified as risk factors in both diseases, but the vast majority of the underlying genetic variation remains to be identified. The objective of CoGIE is to unravel the genetic basis and pathophysiology of IGE and RE establishing a unique interdisciplinary research network of clinicians, geneticists, biostatisticians, physiologists and neuroanatomists.

By using a combination of modern genetic techniques, comprehensive biostatistical analysis and subsequent functional analysis of selected genes and mutations, we aim to reveal new pathophysiological pathways of common idiopathic epilepsy syndromes.

### **Project Leader:**

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### Cover picture:

Kir4.1 immunoreactivity in the mouse hippocampus at postnatal day 42. Perikarya of cells were visualised by Nissl staining (blue), Kir4.1 protein was identified with specific antibodies (green).

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