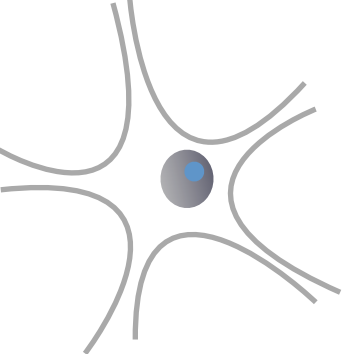


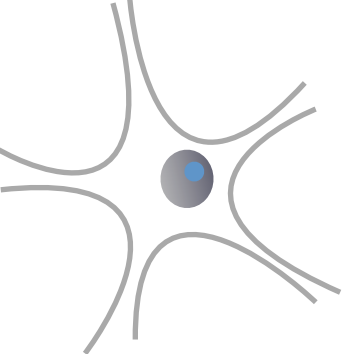
Genetics of the Rare Epilepsy Syndromes



Genetics of Rare Epilepsy Syndromes (RES)

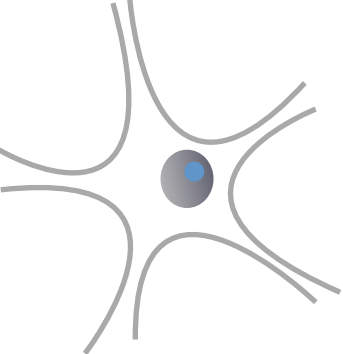
The Epileptic Encephalopathies

EuroEPINOMICS-RES



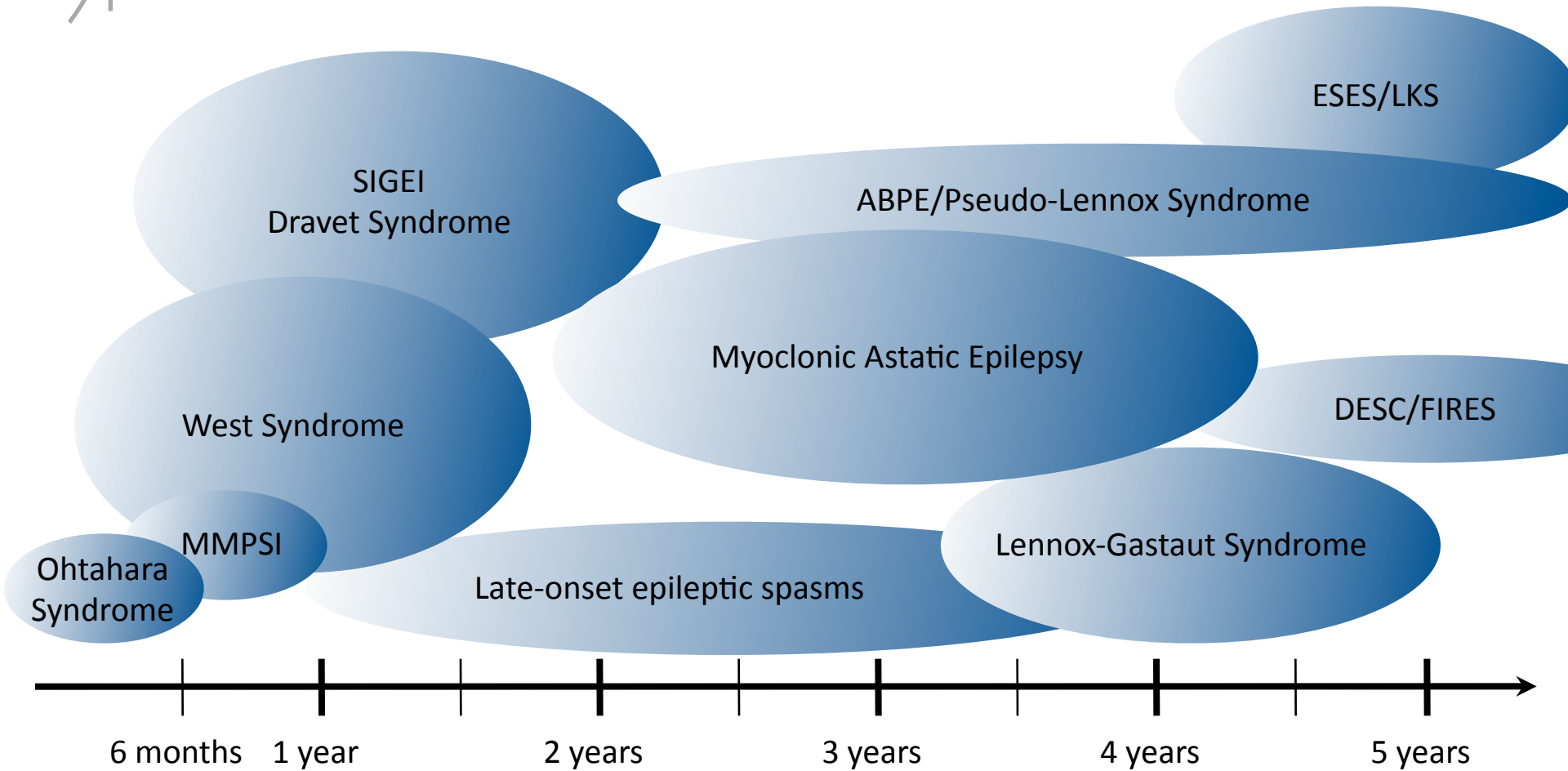
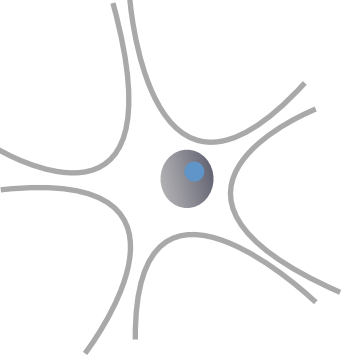
Structure

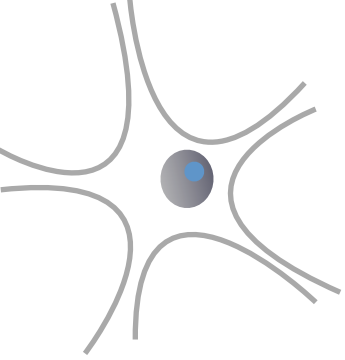
- Epileptic Encephalopathies (EE) as RES
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- The RES Action Plan (Sept 2011)



Structure

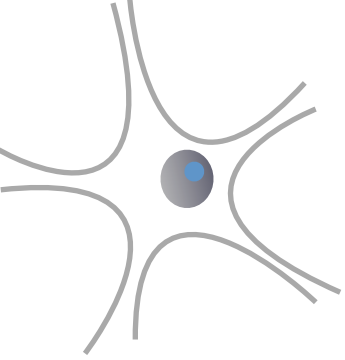
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The Epileptic Encephalopathies

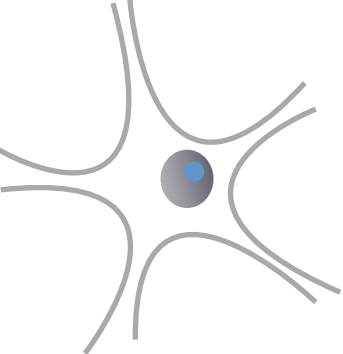
- What are epileptic encephalopathies?
 - Severe, often therapy-resistant epilepsies
 - Epilepsy impacts on development, cognition
- EEs are Rare Epilepsy Syndromes
 - Paradox of Rare Disorders
 - Genetic factors implicated



Genetics of EE

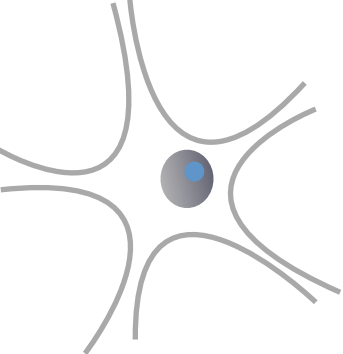
- Many EE are monogenic
 - *SCN1A* -> Dravet Syndrome
 - *STXBP1, ARX, CDKL5*

- EE serve as models for other epilepsies
 - *SCN1A* -> GEFS+
 - 15q13.3 microdel -> IGE



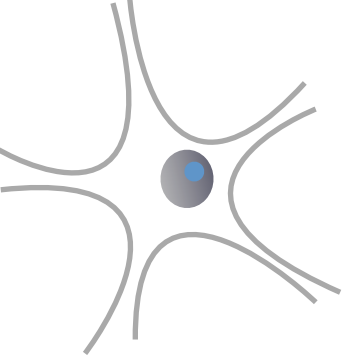
Structure

- Epileptic Encephalopathies (EE) as RES
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- **Aims and structure of the CRP**
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Aims and structure of the CRP

- Central Phenotype Database
 - Phenotypes on 500 patients with EE
 - Web-based, > 200 clinical variables
- Identification of the genetic basis
 - 80-100/500 isolated patients with RES
 - 20 novel epilepsy genes
 - 10 novel disease entities through g/p correlation



500 sporadic RES cases

Phenotyping

Exclusion of relevant known epilepsy genes

IP-02; AP-01: CNV analysis
(array-CGH)

CNV negative

CNV positive

CNVs considered pathogenic if *de novo*,
overlapping with known CNVs or recurrent

Gene discovery

IP-06: Candidate gene panel
AP-02; IP-04; IP-05: Whole exome
sequencing

Gene discovery

IP-01: Candidate genes within the region
AP-04: Modifier genes in recurrent CNVs,
Whole exome sequencing

IP-01, IP-05: Iterative mutation screening in cohorts
with similar phenotypes;
screening of patients with other phenotypes

AP-03: Functional
analysis of variants

IP-01; IP-02; IP-03; IP-10:
Phenotype-genotype
correlation

IP-01; IP-02; IP-03; IP-10:
Diagnostic guidelines

500 sporadic RES cases

Phenotyping

Exclusion of relevant known epilepsy genes

IP-02; AP-01: CNV analysis
(array-CGH)

CNV negative

CNV positive

CNVs considered pathogenic if *de novo*,
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Gene discovery

IP-06: Candidate gene panel
IP-02; IP-04; IP-05: **Whole exome
sequencing**

Gene discovery

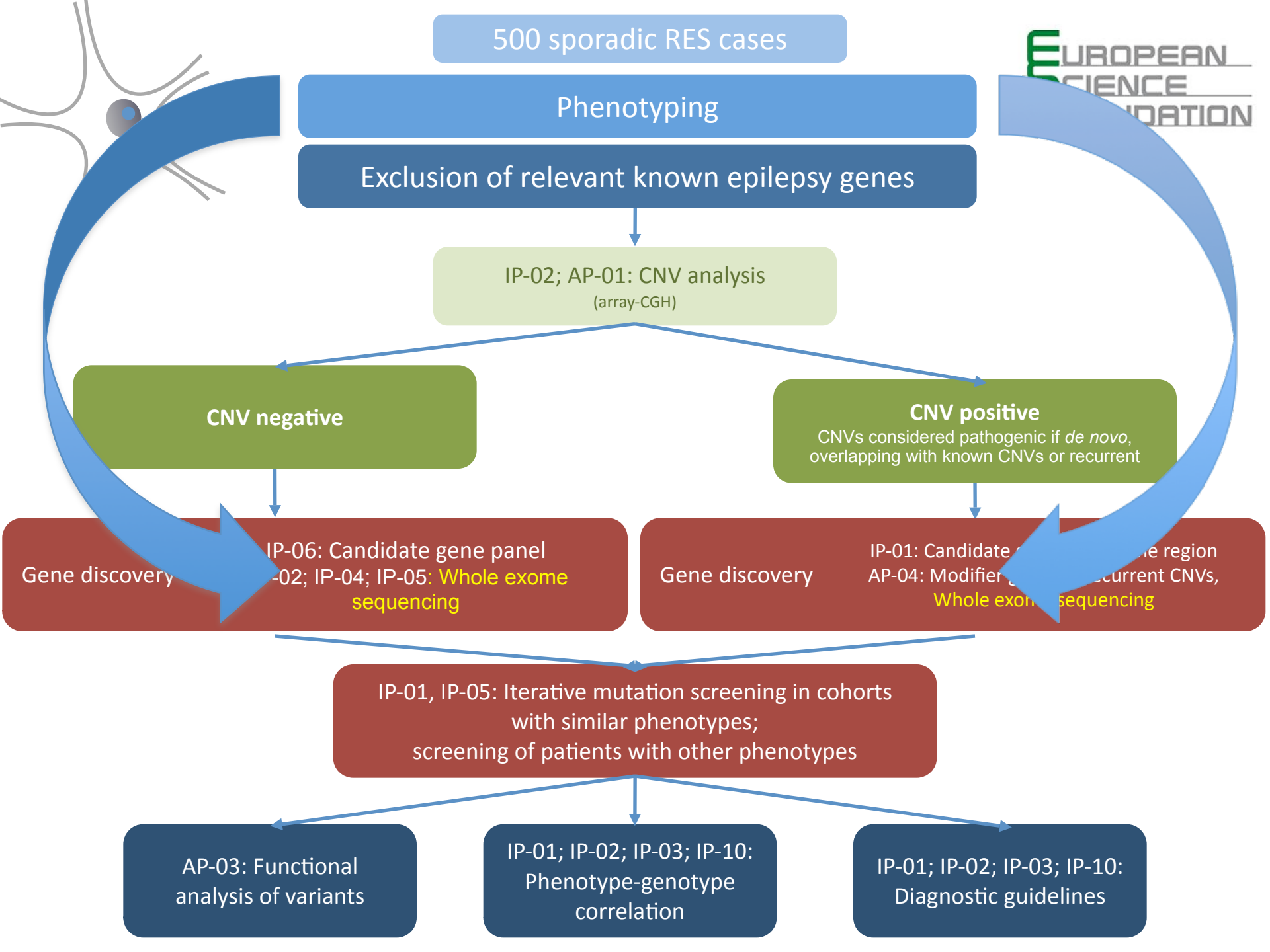
IP-01: Candidate gene panel in the region
AP-04: Modifier genes in recurrent CNVs,
Whole exome sequencing

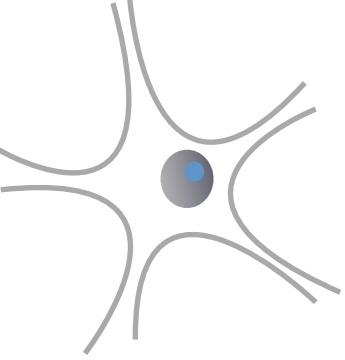
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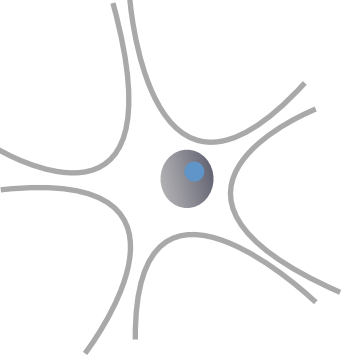
IP-01; IP-02; IP-03; IP-10:
Diagnostic guidelines





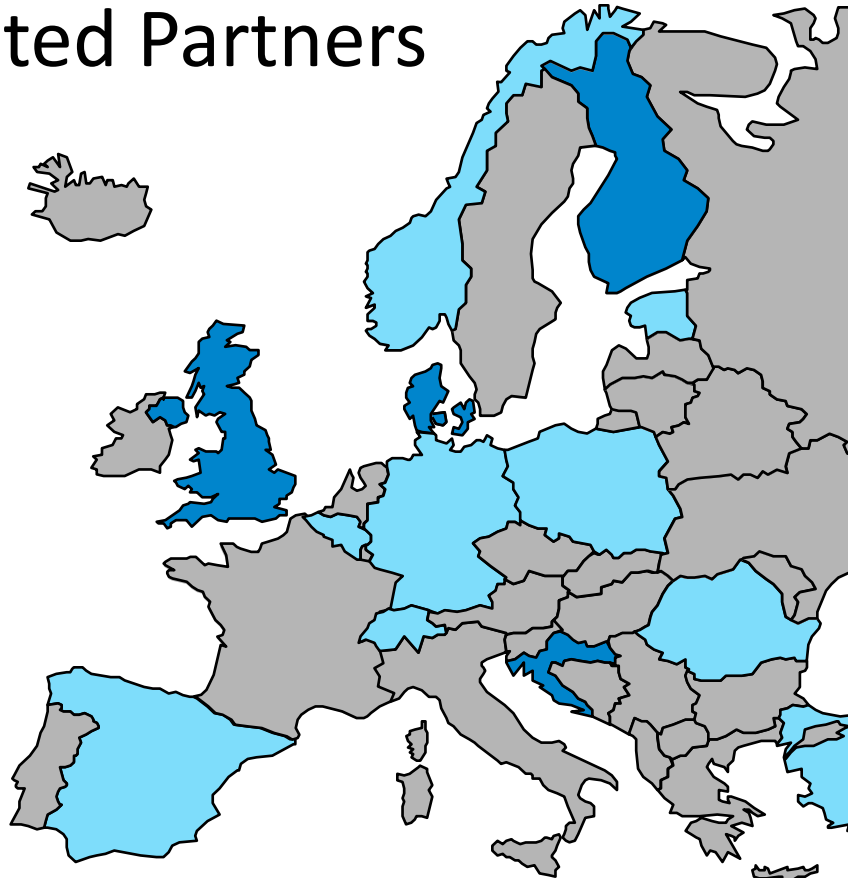
Structure

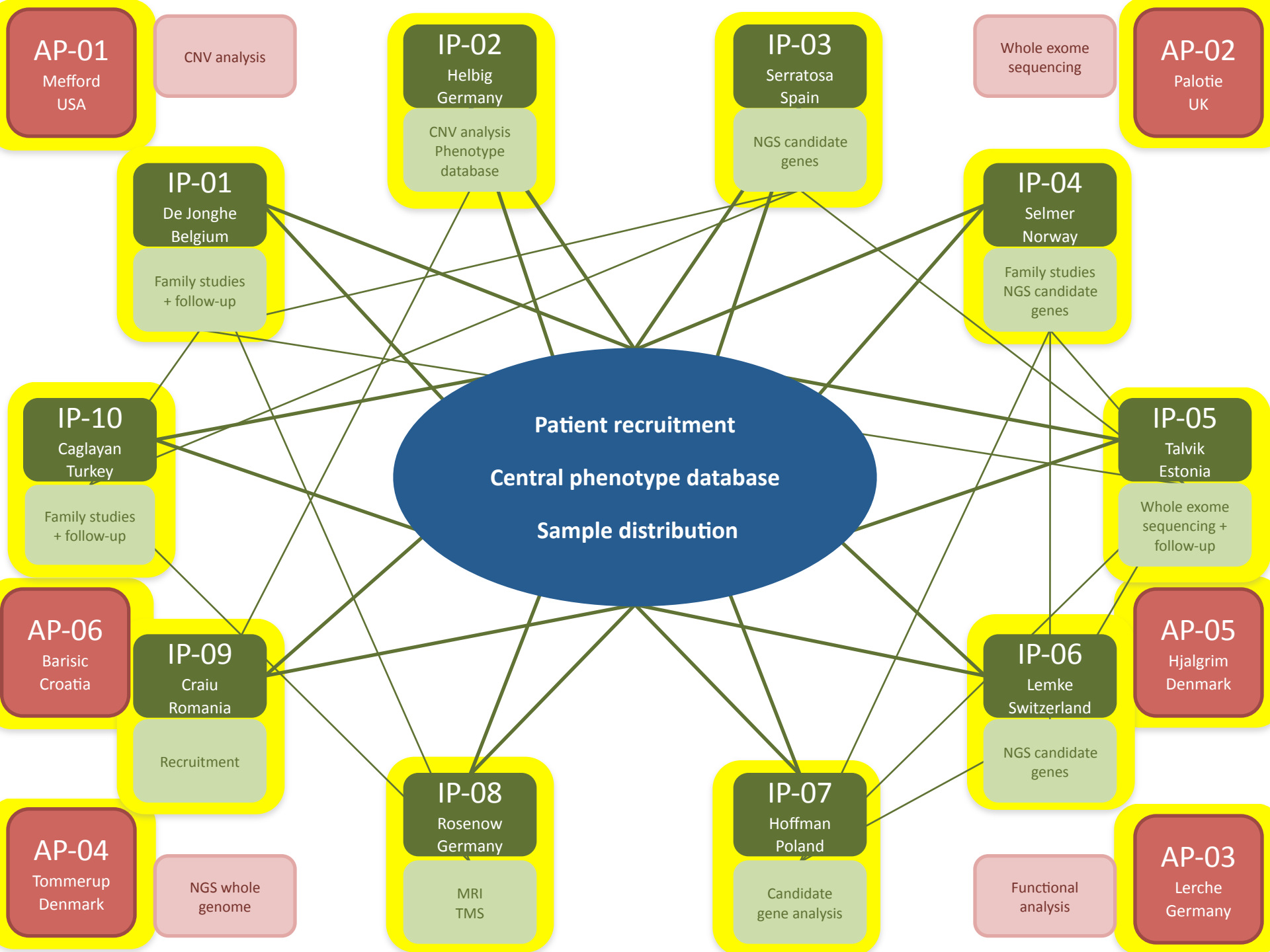
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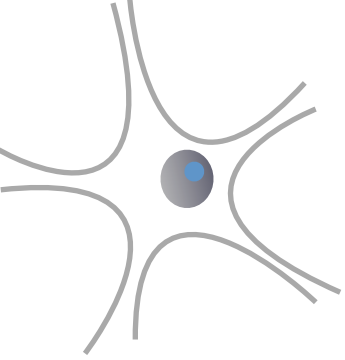


Structure of the CRP

- 10 Individual Projects
- 6 Associated Partners

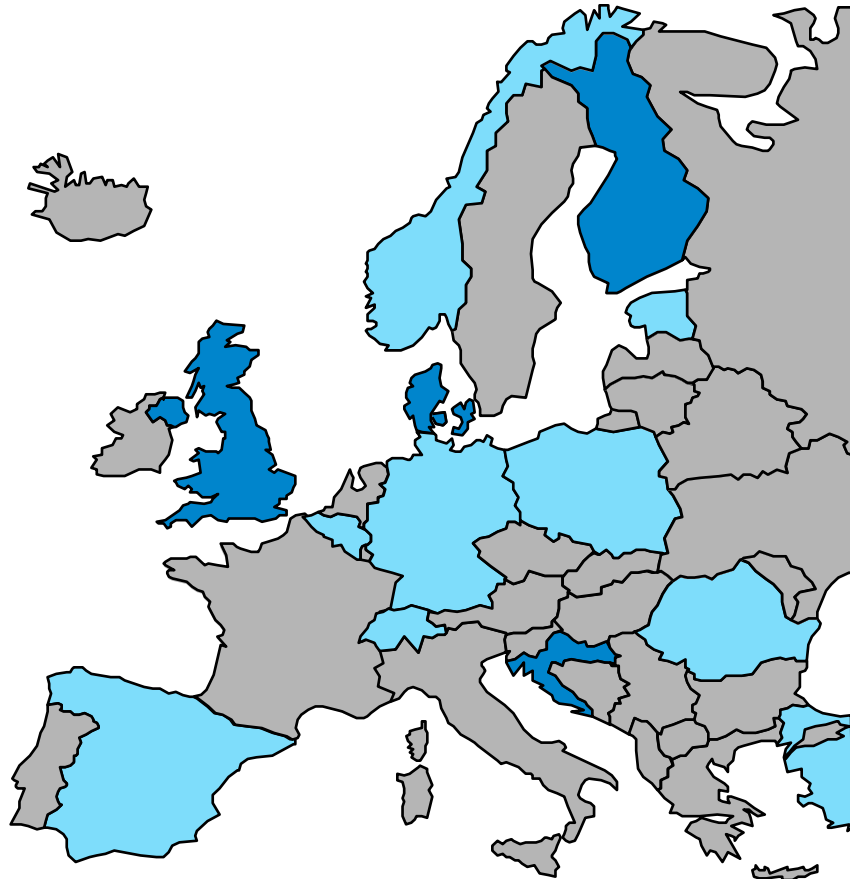






Infrastructure for CRP

- Central Genotype/Phenotype database



Cartagenia Bench

Lab shortcuts



To Folders



Upload a file



Filter and label



Array-CGH



Next-Gen Sequencing



Locus-specific assays



To Toolbox

Clinic shortcuts



Patients



Advanced search



Report generator



Manage CNV sets



Genome annotation



Assay request and referral



to DECIPHER



to NCBI



Share within consortium

Settings and Help



Administration



User Settings



Log Out



Users and access rights



Project management



Manage CNV labels



Create Helpdesk ticket



Help













BENCH-RES - Central Genotype/Phenotype database

Created by: svanvoor on 19-sep-2011
Last updated by: svanvoor on 19-sep-2011
In project: Epilepsy cases
Comment:

- Overview
- Description
- Clinical data
- Phenotype**
- Genotype
- Pictures
- Family
- Reporting
- Add to selection

Patient phenotype information

Phenotype traits

- EPOID:0000043 **Myoclonic atonic**   
- EPOID:0000061 **Myoclonic Astatic Epilepsy (MAE)**   
- EPOID:0000019 **Generalised tonic-clonic seizures**   
- EPOID:0000056 **photosensitivity: Grade 1**   

Search phenotype traits

EPO

Start typing part of the phenotype you are looking for in the box above.

Browse

Ontology: EPO (click to show/hide)

- EEG features
 - photosensitivity
 - photosensitivity: Grade 2
 - photosensitivity: Grade 1
 - photosensitivity: Grade 4
 - photosensitivity: Grade 3
 - generalised discharges
 - irregular spike-wave discharges
 - regular spike wave discharges
 - background rhythm
- Syndromes
- Seizure types
- Imaging

Onset and clinical course

Search modifiers




















Epilepsy modifiers

Browse

Ontology: Epilepsy modifiers (click to show/hide)

- MRI, EEG modifiers
- seizure type modifiers
 - age of offset
 - age of onset
 - onset adult, unknown
 - onset > 20 years
 - onset unknown
 - onset 15-20 years
 - onset neonatal
 - onset 1-3 months
 - onset 3-6 months
 - onset 6-12 months
 - onset 1-2 years
 - onset 2-4 years
 - onset 10-15 years
 - onset 4-6 years
- frequency
- response to medication

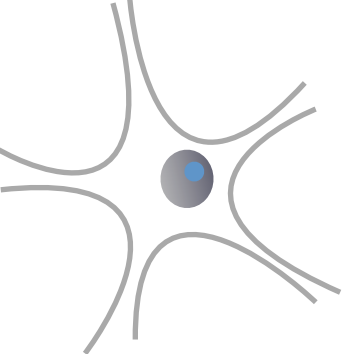
Cartagenia Bench

Lab shortcuts			Clinic shortcuts			Settings and Help			
 To Folders	 Upload a file	 Filter and label	 Patients	 Advanced search	 Report generator	 Administration	 User Settings	 Log Out	
 Array-CGH	 Next-Gen Sequencing	 Locus-specific assays	 Manage CNV sets	 Genome annotation	 Assay request and referral	 Users and access rights	 Project management	 Manage CNV labels	
 To Toolbox			 to DECIPHER	 to NCBI	 Share within consortium	 Create Helpdesk ticket	 Help		

Cartagenia BENCH Release June-2011 - Using: GRCh37/hg19 - Ensembl v54 - DGV November 2010 - PubMed April 2011 - Release notes

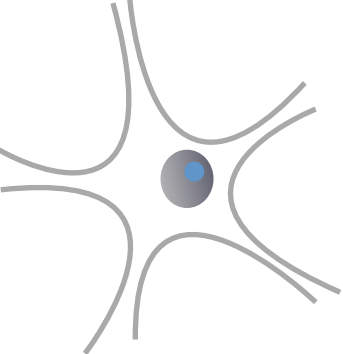
Copyright © 2011 Cartagenia

- BENCH-RES** - Central Genotype/Phenotype database
- Standardized phenotyping language
- Filter, search functions, ontology-based phenotyping



Structure

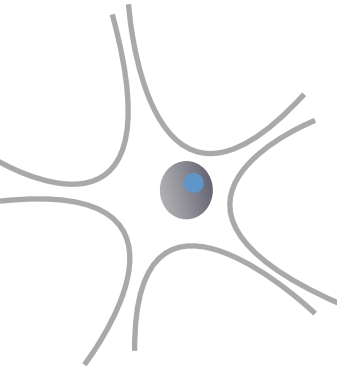
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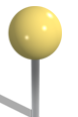


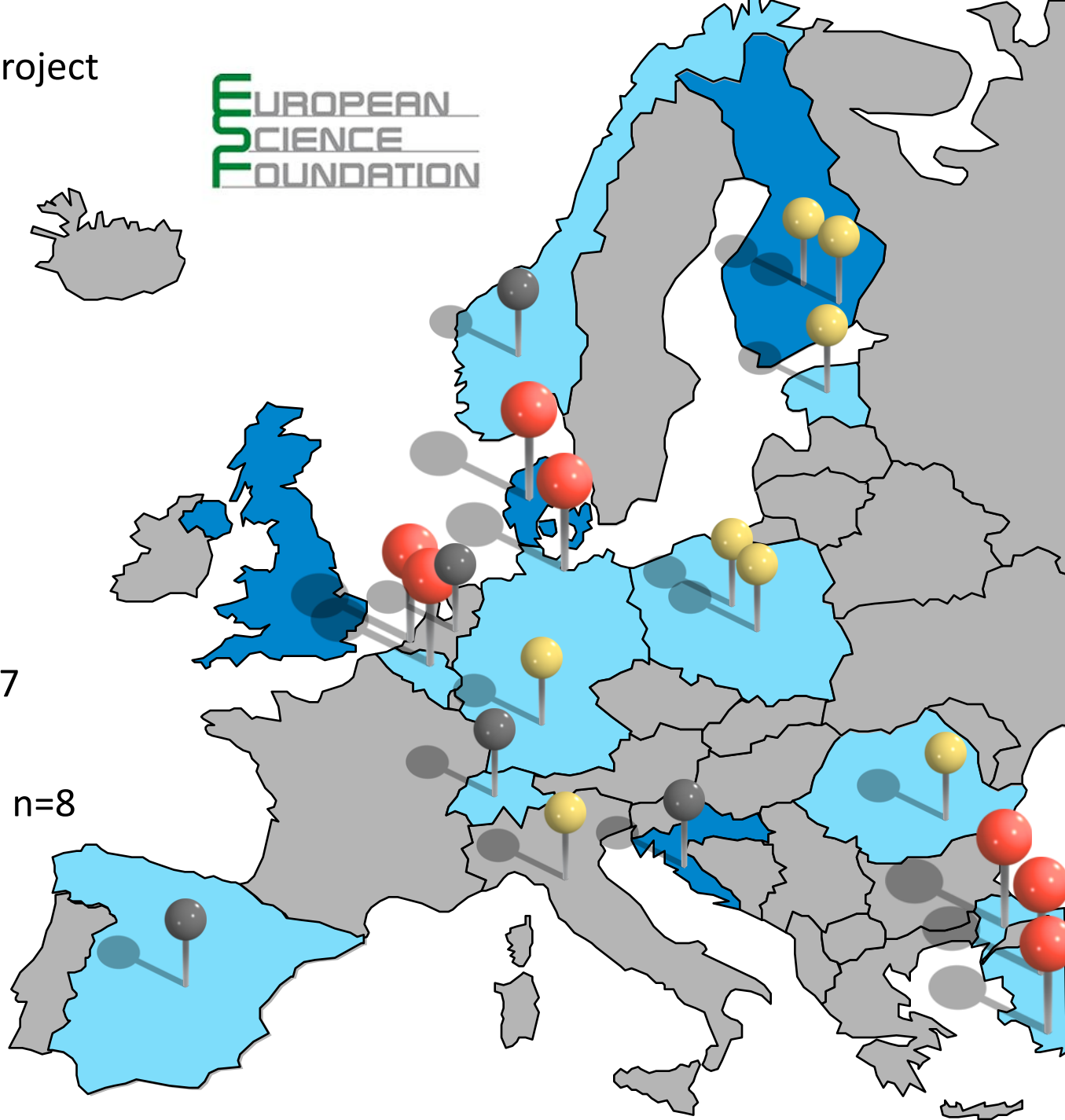
RES Action plan on EE

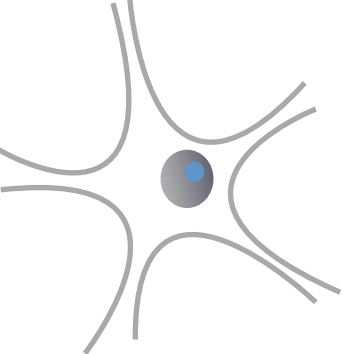
- Pioneer project
 - *SCN1A*-negative Dravet Syndrome
 - Exome Sequencing of complete trios
 - Deadline Oct 15th, 2011

SCN1A-negative-Dravet-Project
State of Recruitment



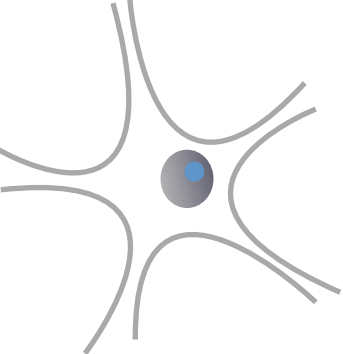
-  complete trios n=7
-  currently recruited n=8





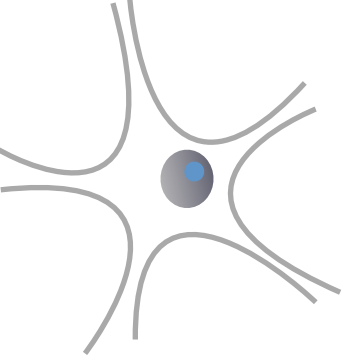
RES Action plan on EE

- Pioneer project
 - *SCN1A*-negative Dravet Syndrome
 - Exome Sequencing of complete trios
 - Deadline Oct 15th, 2011
- Exome sequencing in Infantile Spasms
 - 60 – 80 trios, Deadline Nov 15st, 2011
- Other epileptic encephalopathies
 - MAE, LGS, CSWS (call for samples prior to Antwerp)



Resources available

- CNV analysis through AP-01 (Mefford)
 - 200-300 samples from IPs/APs
 - Phenotypic information in database (CPD)
- *SCN1A* sequencing of Dravet Syndrome
 - IP-01 (De Jonghe), 50 samples
 - Trios with parents required
 - Phenotypic information in database (CPD)



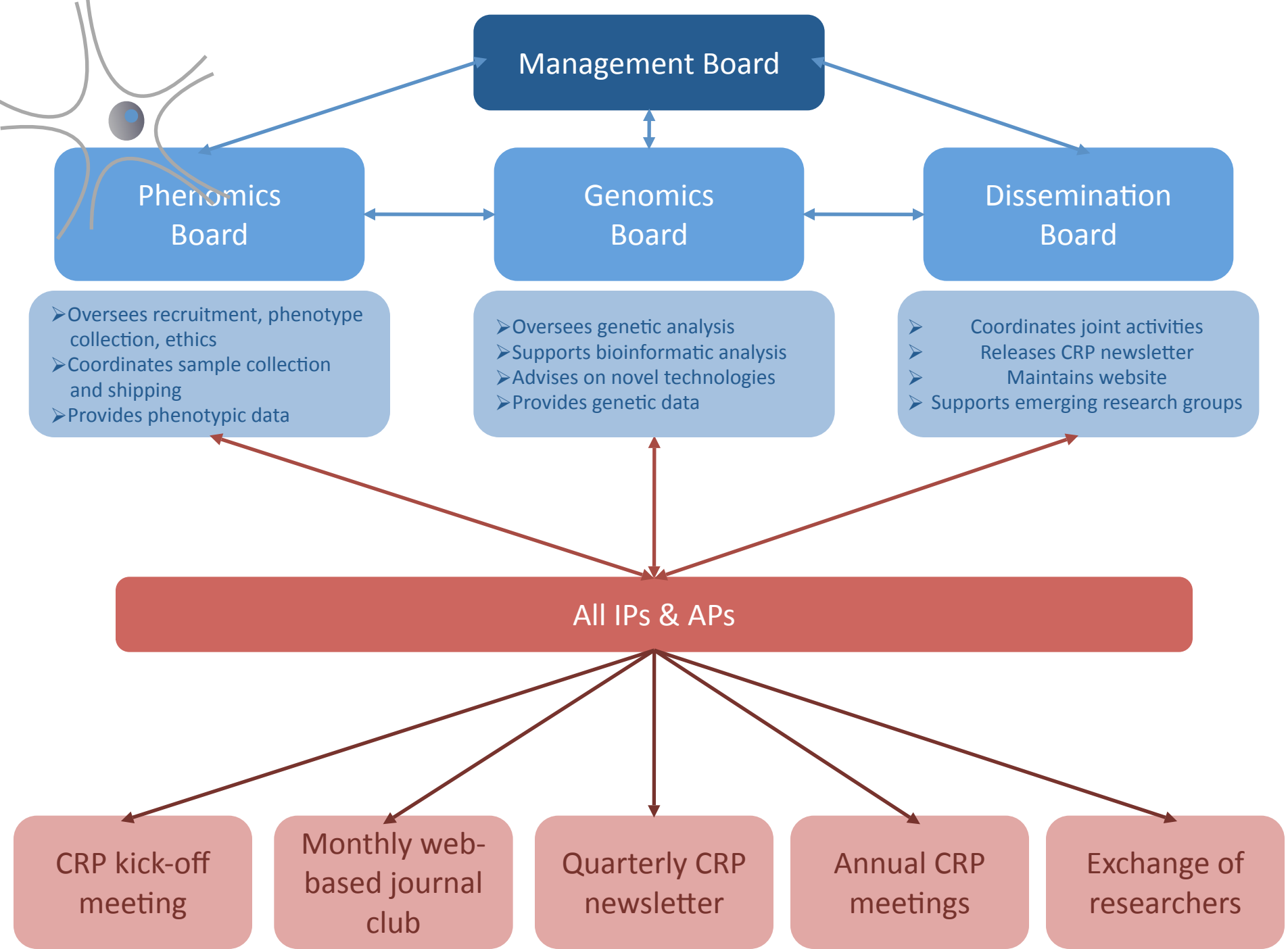
RES Kick-off meeting

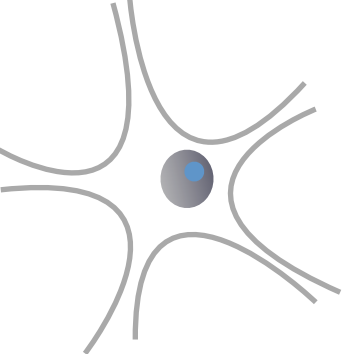
EUROPEAN
SCIENCE
FOUNDATION

EuroEPINOMICS
networking
activity

- Antwerp meeting
 - Nov 17th-18th, 2011
 - Please register by **Sept 30th, 2011**
 - www.euroepinomics.org

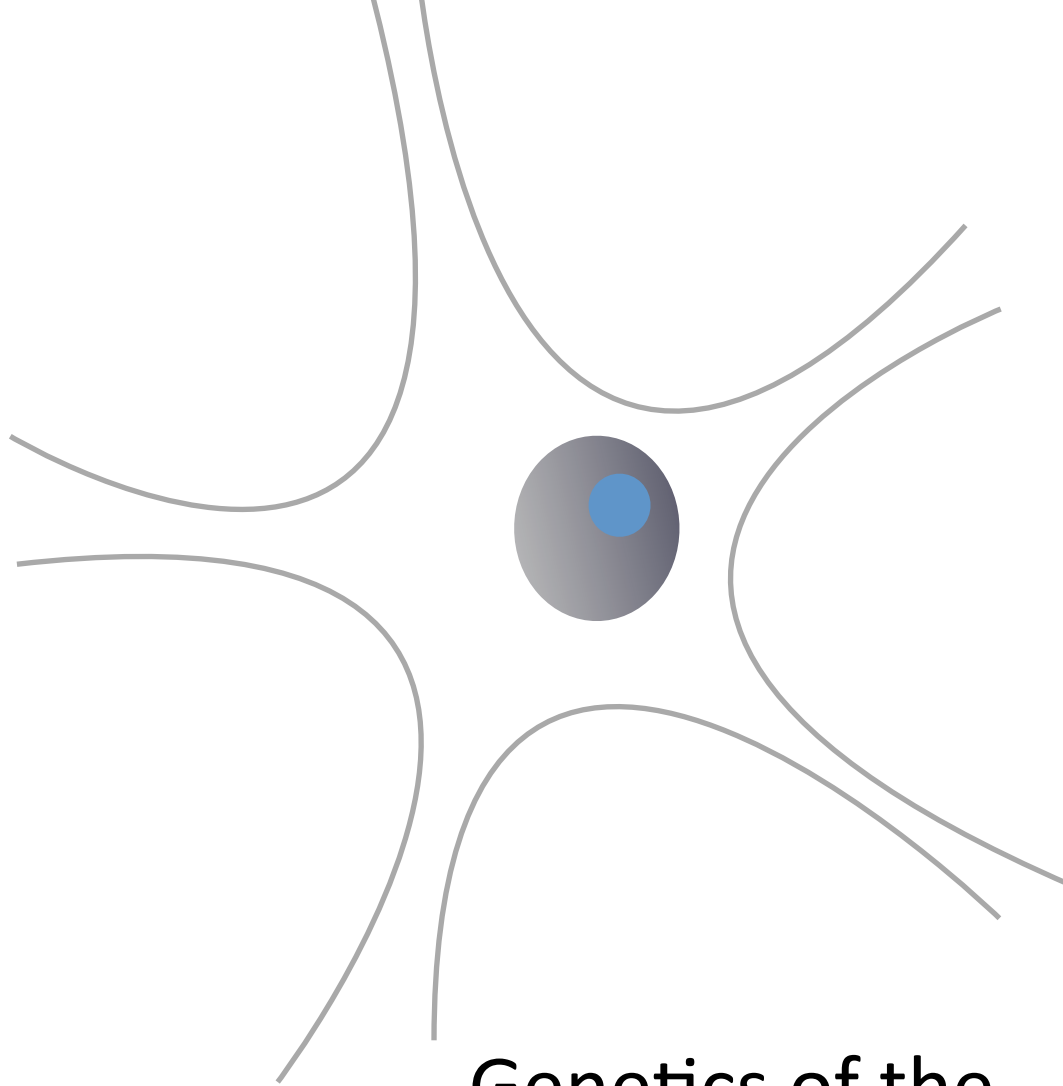






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 - Please remember the Sample Custodian Forms



Genetics of the Rare Epilepsy Syndromes