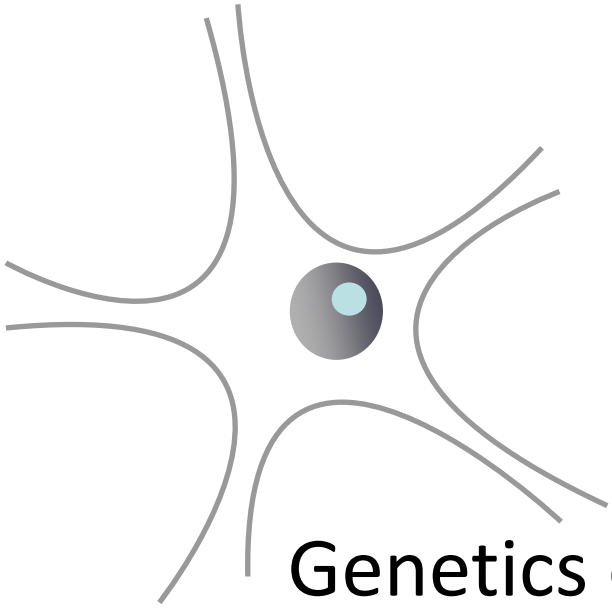


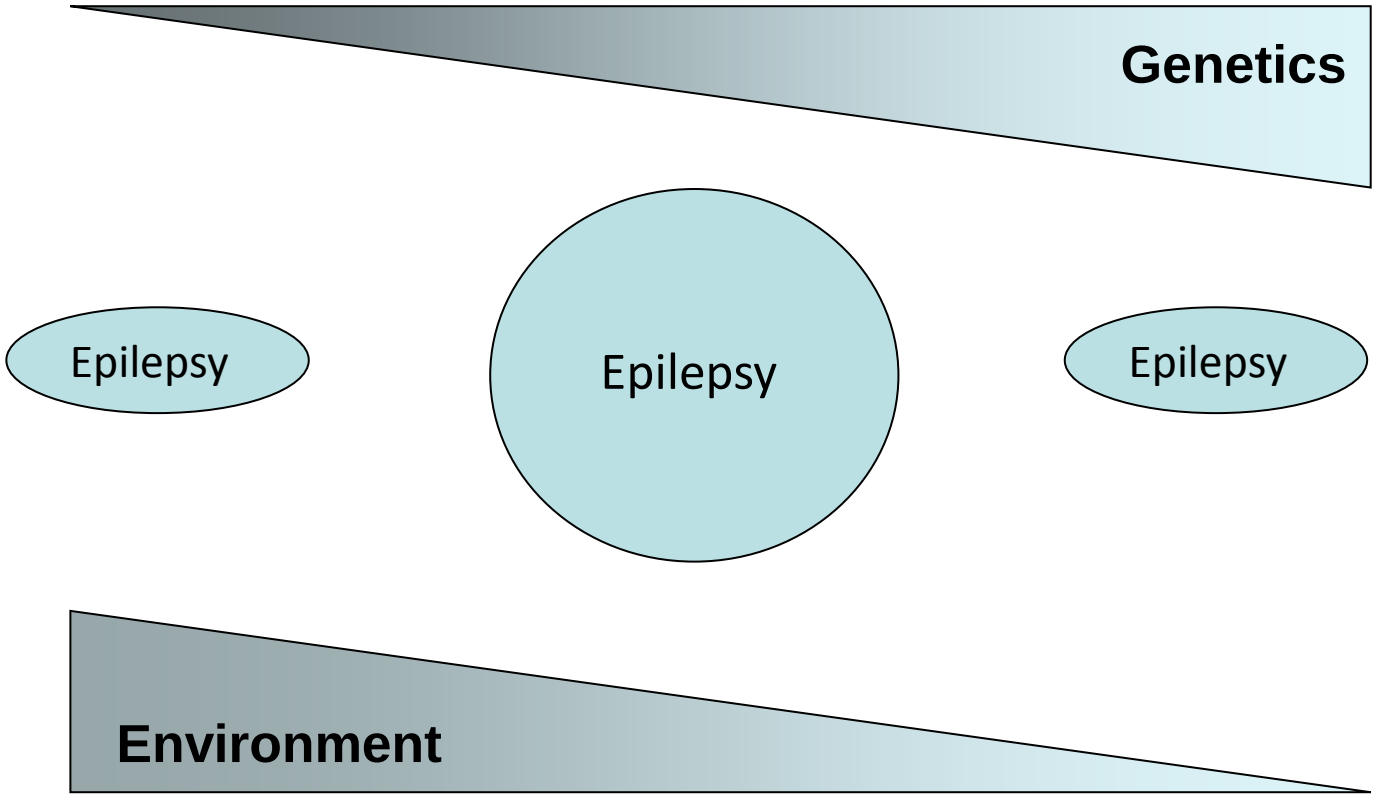
Genetics of Epilepsy – a clinical research project

Dag Undlien
Dep. of Medical Genetics
Oslo University Hospital

Epilepsy

- Prevalence of ~1%
- Risk for siblings: 3-6%
- Concordance rates MZ twins >> DZ twins

Genetics of epilepsy



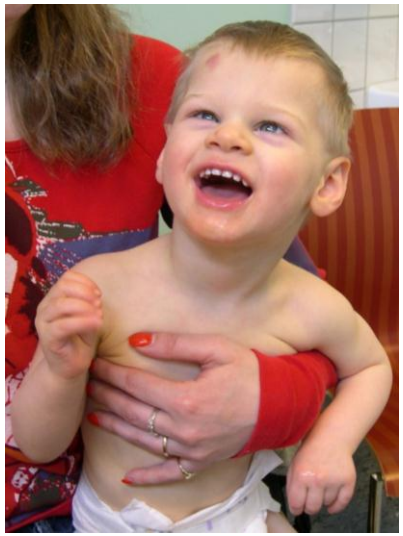
Genetics of epilepsy

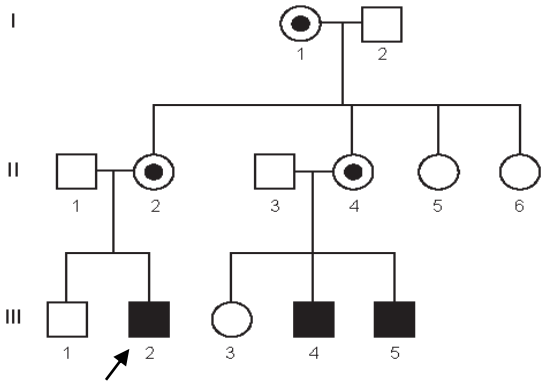
- A group of heterogeneous disorders
- Most epilepsies are multifactorial
- Some are caused by mutation in one gene alone: Monogenic

Genetics of monogenic epilepsies

Epilepsy syndrome	Chromosomal position	Gene
ADNFLE	20q13.3	CHRNA4
Autosomal dominant nocturnal frontal	1q21.3	CHRNB2
lobe epilepsy	8p21.2	CHRNA2
BFNC	20q13.3	KCNQ2
Benign familial neonatal convulsions	8q24.2	KCNQ3
BFNIS	2q24.3	SCN2A
Benign familial neonatal-infantile seizures		
GEFS+	2q24.3	SCN1A
Generalized epilepsy with febrile	19q13.1	SCN1B
seizures plus	5q34	GABRG2
DS	2q24.3	SCN1A
Dravet syndrome		
JME	5q34	GABRA1
Juvenile myoclonic epilepsy	2q23.3	CACNB4
	3q27.1	CLCN2
	6p12.2	EFHC1
ADPEAF	10q23.3	LGI1
Autosomal dominant partial epilepsy with auditory features		

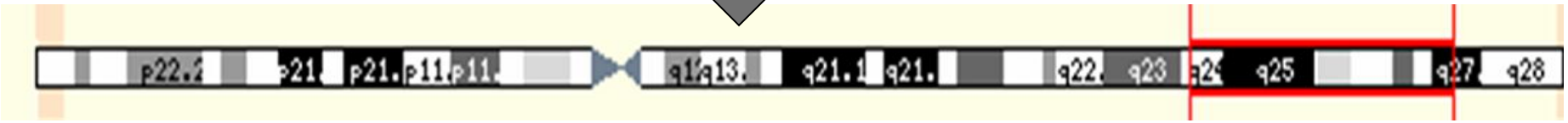
Traditional mapping of epilepsy genes: Linkage analysis





Identify phenotype

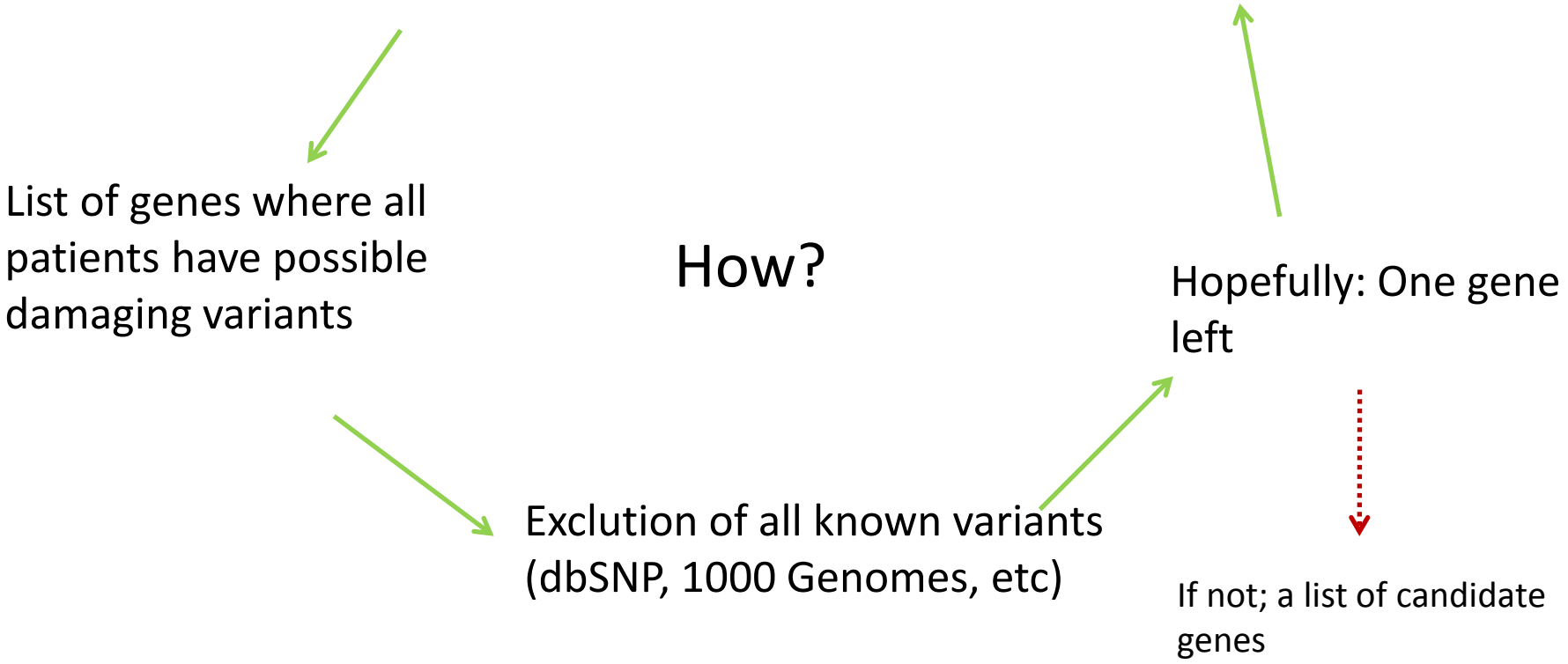
Collect family data and DNA



Do linkage analysis, sequence candidate genes and find causal mutation

Modern mapping of epilepsy genes

1. Find patients w/same phenotype
2. Sequence entire genome or exome → find causal mutation



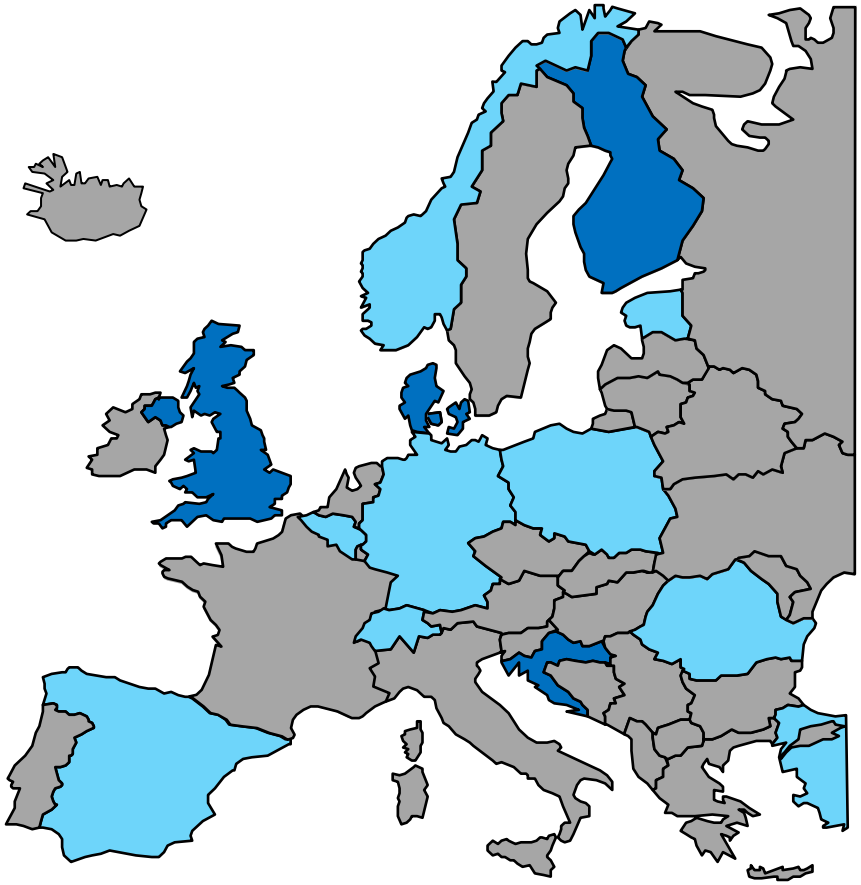
Challenges

- Monogenic syndromes are rare
- Epilepsy is heterogeneous
- Technical issues concerning sequencing
- How to deal with incidental findings in a good way. Return of results policies
- Data sharing

EuroEpinomics – a large European collaboration

- Aim: Find and characterize epilepsy genes
- 14 research groups from 12 different countries
- Join forces and patient groups

- INCREASED POWER



EuroEpinomics – Rare Epilepsy Syndromes

- Modern mapping approach on joined patient groups using exome sequencing of families and sporadic cases
- Additionally
  - Copy number variations
  - Functional experiments
  - Genotype phenotype correlations
- Common clinical database

How to deal with incidental findings?

The New York Times

Genes Now Tell Doctors Secrets They Can't Utter

Gretchen Ertl for The New York Times

Dr. Robert C. Green of Harvard sees practical and ethical issues in trying to warn anonymous study subjects of disease risks.

By GINA KOLATA
Published: August 25, 2012

Dr. Arul Chinnaiyan stared at a printout of gene sequences from a man with cancer, a subject in one of his studies. There, along with

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THIS WEEK

EDITORIALS

HIGGS Would a boson by another name smell as sweet? p.374

WORLD VIEW Rio summit demands a different science approach p.375

TASTELESS Bottl dolphins get littl from food p.377

Incidental benefits

Scientists who screen the genes of volunteers for research should tell participants if they find information relevant to their health.

Nature 2012

Ethical and legal challenge.

Filtering away ”bad genes” as a means to minimize the risk of incidental findings?

Pros

- Can eliminate some incidental findings
  - Minimize ethical challenges
- May remove potential IFs ”permanently” including future use

Cons

- Genes can have pleiotropic effects
  - Eg mutations in Lamin A can lead to 9 different diseases
- ”Anti-research” in nature
- Hard policy to maintain over time
  - Reanalysis of data important
  - Increasing knowledge of genome function

”Procedural filtering”

- Several possibilities
  - Using healthy relatives as ”negative filters”
  - Only including genes were thera are deleterious variants in many patients
  -
  - ++
- Does not hamper research efforts/inherent to research strategy
- Future use of data/data sharing?

Informed consent

- No systematic search for specific incidental findings will be performed – some ”procedural filtering”
- Offered return of results of medically actionable incidental findings. Patients can opt out of getting results
- Separate question on incidental findings with consequences for family planning (carrier status etc)
- Separate ”ethical” review board will be consulted before return of results are given
- Return of results to children (<16 years) will only be considered if it has consequences for treatment
- Before final return of results a new sample must be analyzed in a diagnostic lab

Collaborators

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