EpiCARE ERN EDUCATIONAL WEBINARS

Introduction to genetic counseling

for epileptic disorders

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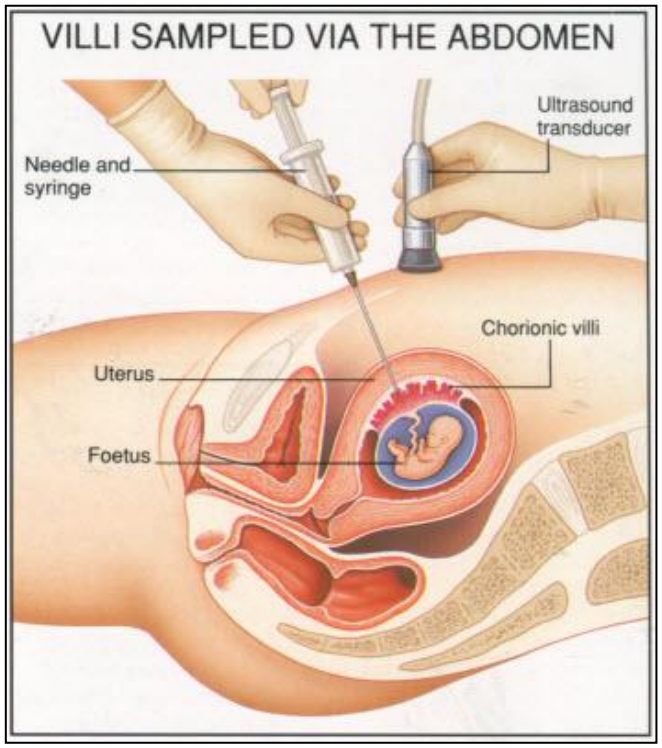
Co-founded by the EU

Genetic counseling: definition

- Process by which the patients, or relatives at risk of an inherited disorder, are advised of:
  - the consequences and nature of the disorder
  - the probability of developing or transmitting it
  - the options open to them in management and family planning
- Accurate genetic counseling is based on the identification of disease causing genetic or chromosomal variants

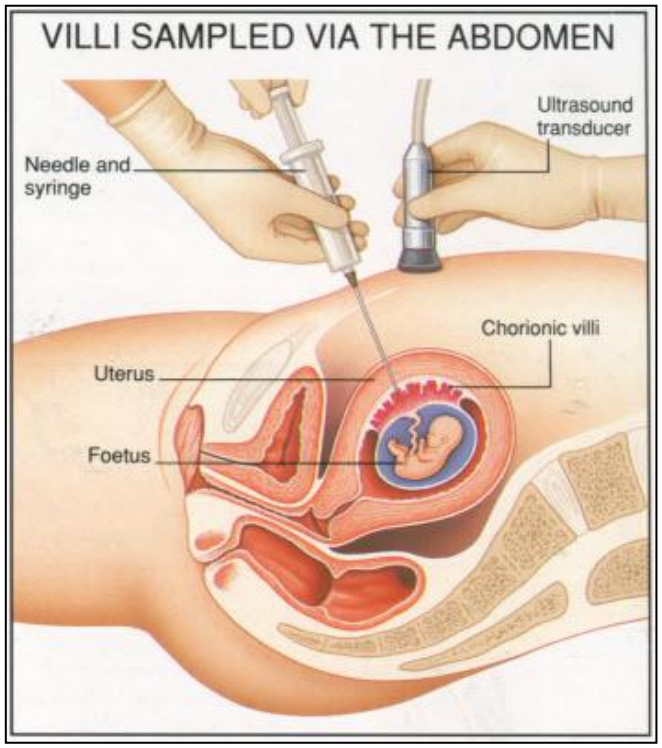
Procreation options for families affected with Mendelian epilepsies with severe outcome

Prenatal diagnosis



11 weeks of amenorrhea

Prenatal diagnosis



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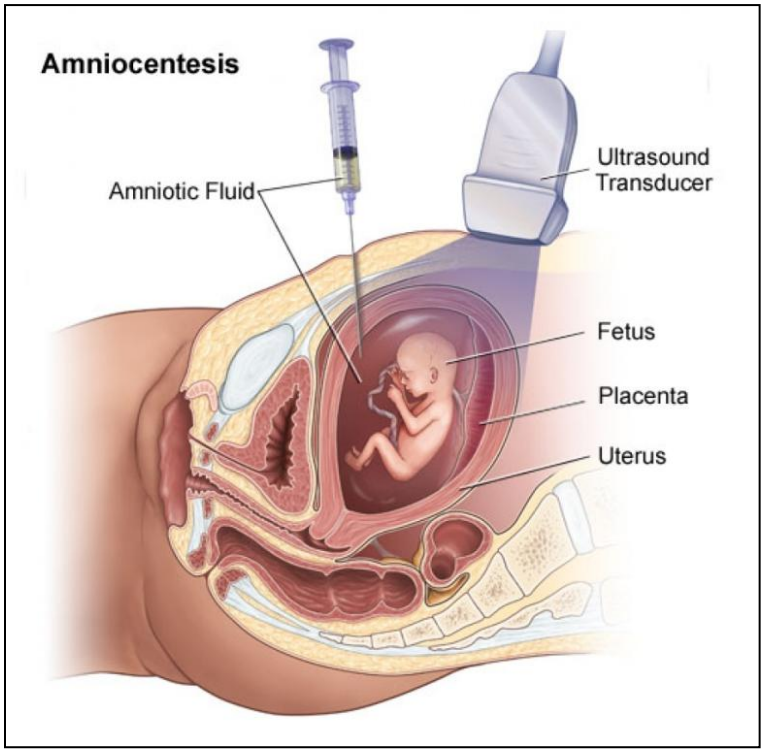
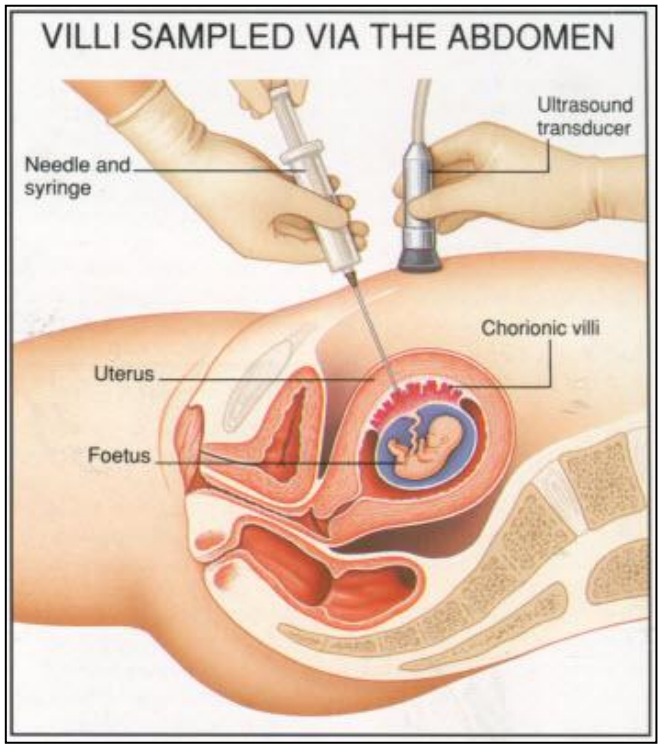


15 weeks of amenorrhea

Prenatal diagnosis



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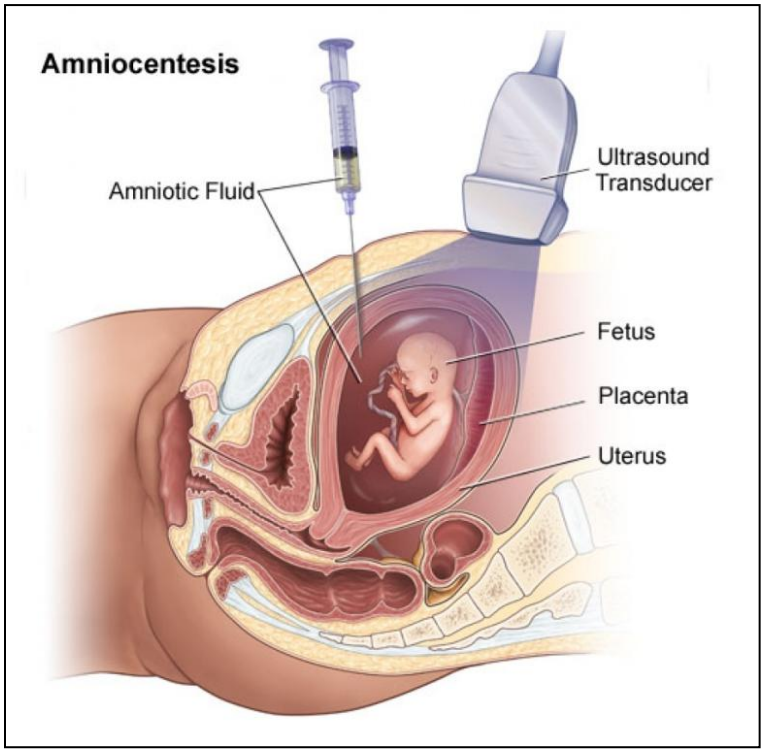
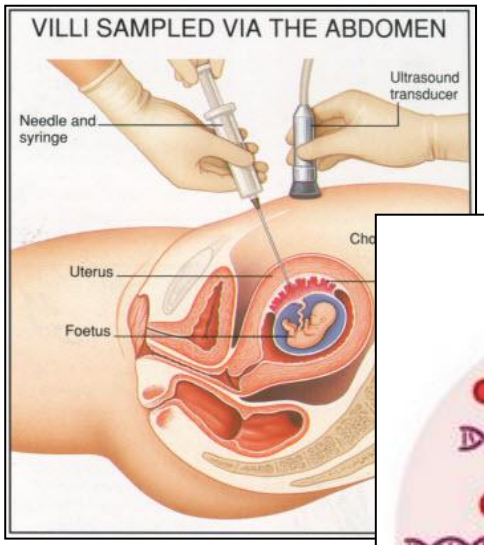


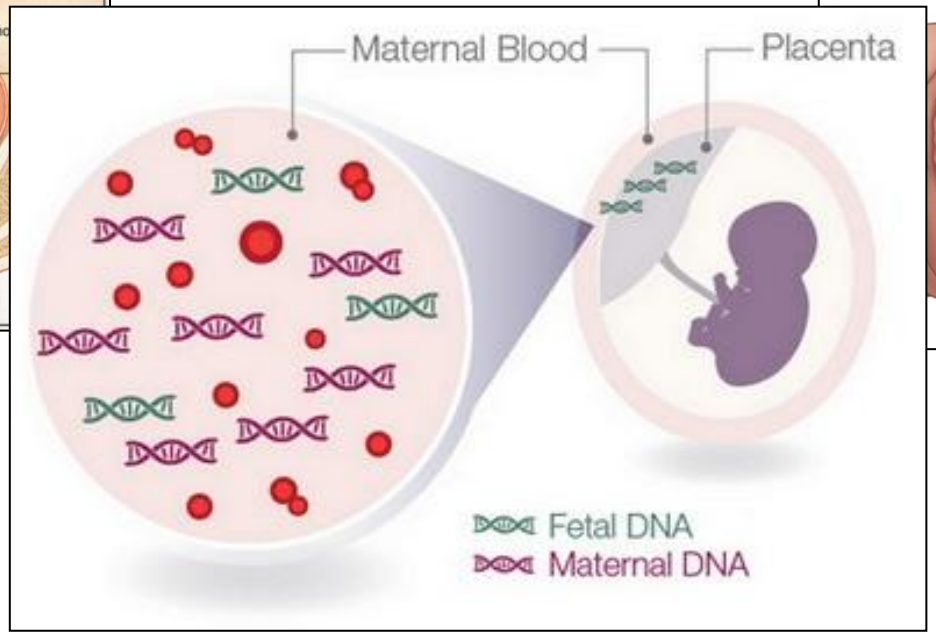
15 weeks of amenorrhea

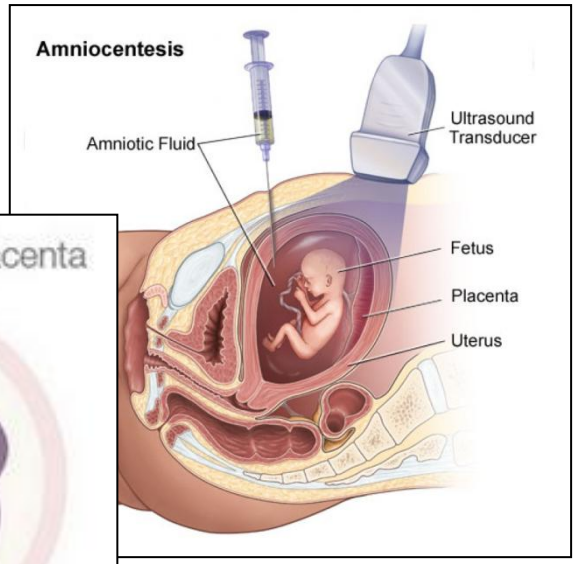
Requires definite genetic diagnosis in the index case and determination of parental status

Prenatal diagnosis



10 weeks of gestation

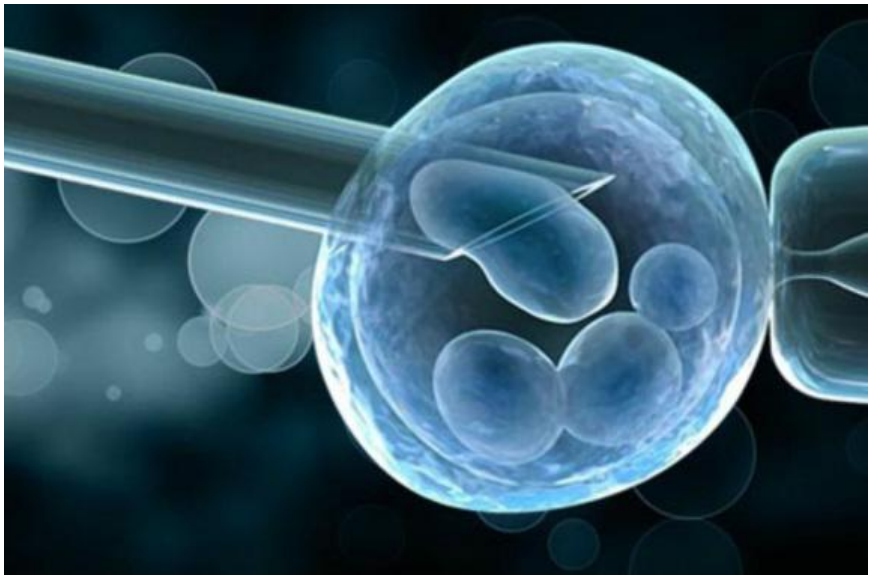




- For X-linked disorders it is possible to perform fetal sex determination in maternal blood before PND

Preimplantation genetic diagnosis

- In vitro fertilization
- Genetic study in 1 blastocyst cell
- Same conditions as PND but only for inherited diseases
- Mother < 40 years of age



Favorable situations for PND/PID

- Mendelian or chromosomal disorders: a gene or chromosomal variant is highly related to disease
- Best configuration:
  - High penetrance
  - Homogeneous expressivity
  - Good genotype phenotype correlations
  - X-linked recessive disorder (females not usually affected)

The two main categories of genetic factors

Strong influence of a major gene

Mendelian epilepsies

High amplitude effect, high risk of disease

Limited influence of a given gene

Multifactorial epilepsies

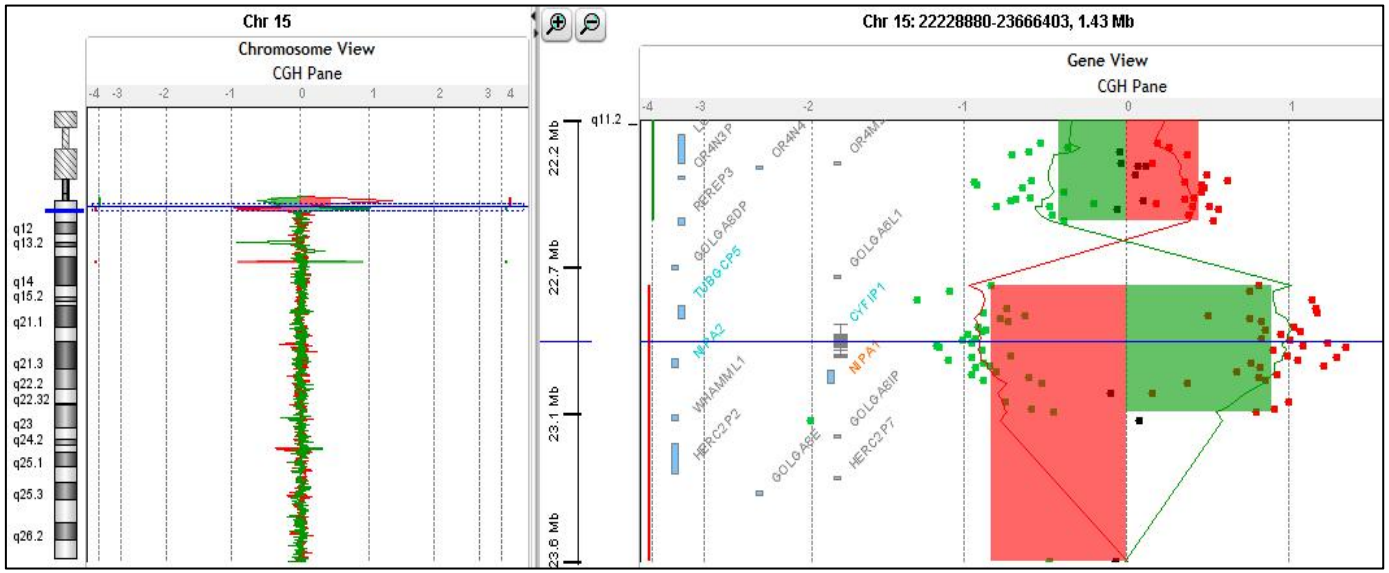
Risk factors, neither necessary nor sufficient

“Idiopathic”/genetic generalized epilepsy

- Often familial occurrence
- Higher risk to be have epilepsy for 1st degree relatives of patients
- **But** rarely consistent with a Mendelian mode of inheritance
- Usually multifactorial inheritance with several genetic risk factors and environmental factors

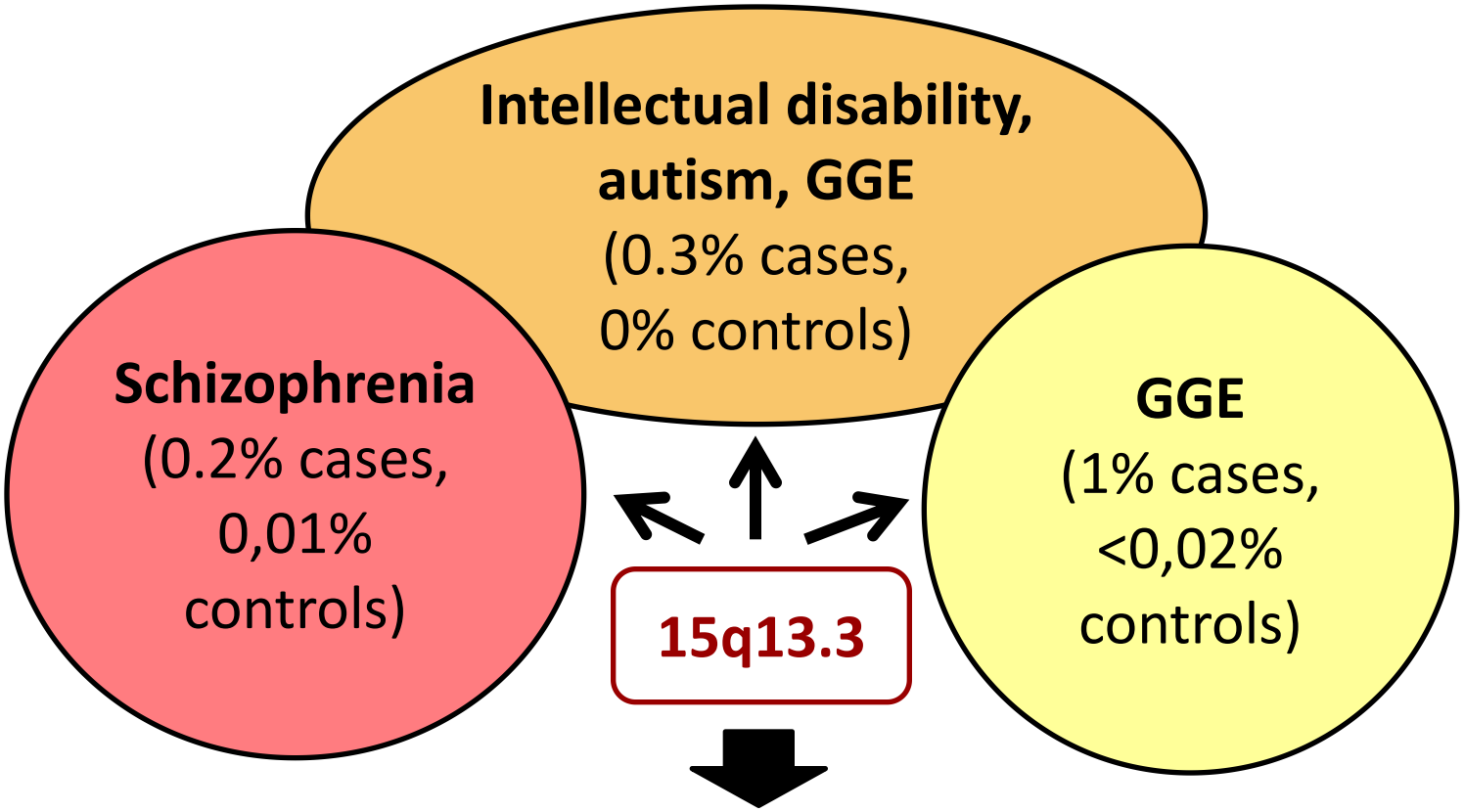
Genetic risk factors and GGE

- Female, 2 years: absence epilepsy with falls -> remission (valproate discontinued)
- 6 years: childhood absence epilepsy -> remission (stop discontinued)
- 13 years: myoclonia at awakening, 2 GTCS
- No cognitive impairment
- No family history of epilepsy



15q13.3 microdeletion

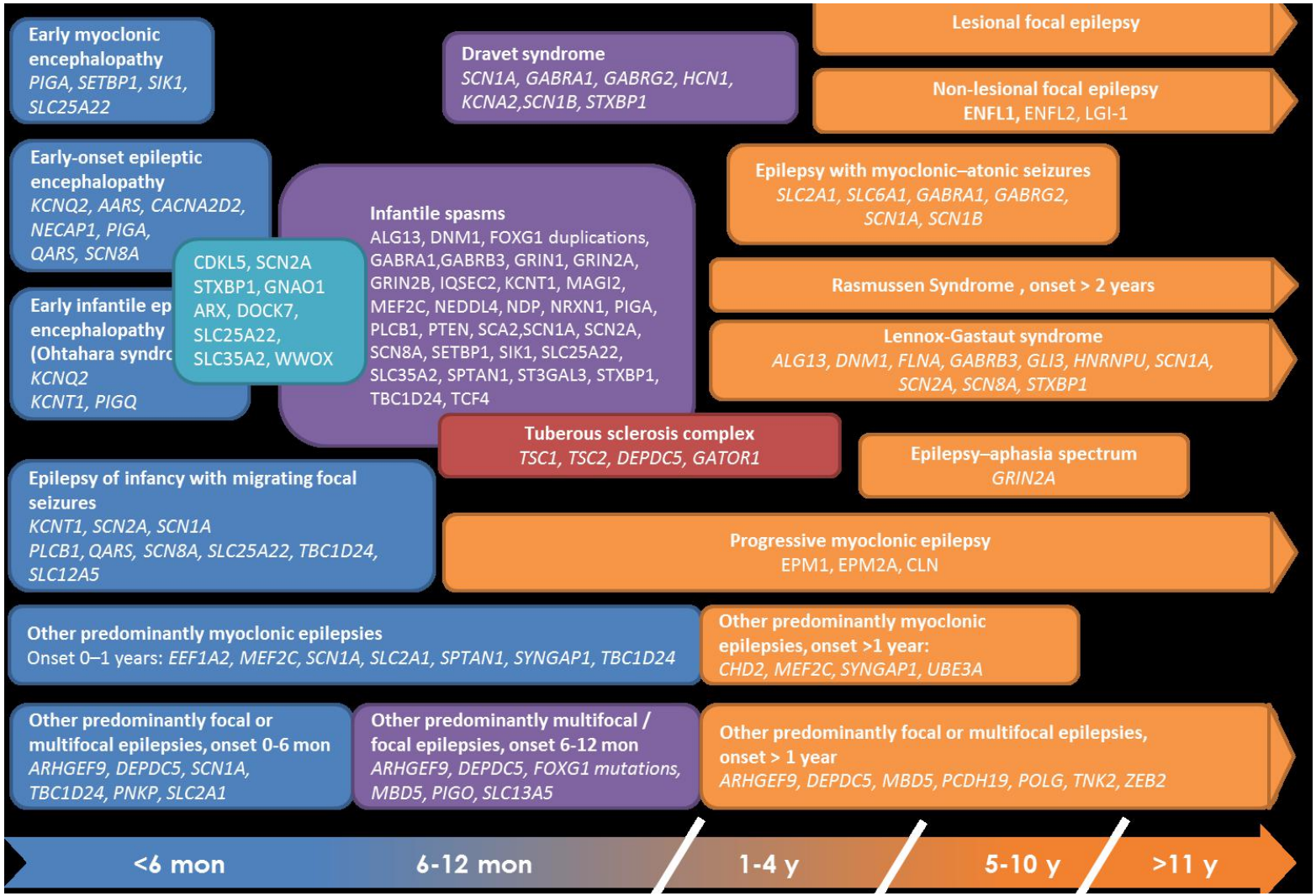
Variability of clinical expression of the 15q13.3 microdeletion



Odds ratio : 68 [29 – 181]

Inherited in 80% of cases (half of them unaffected)

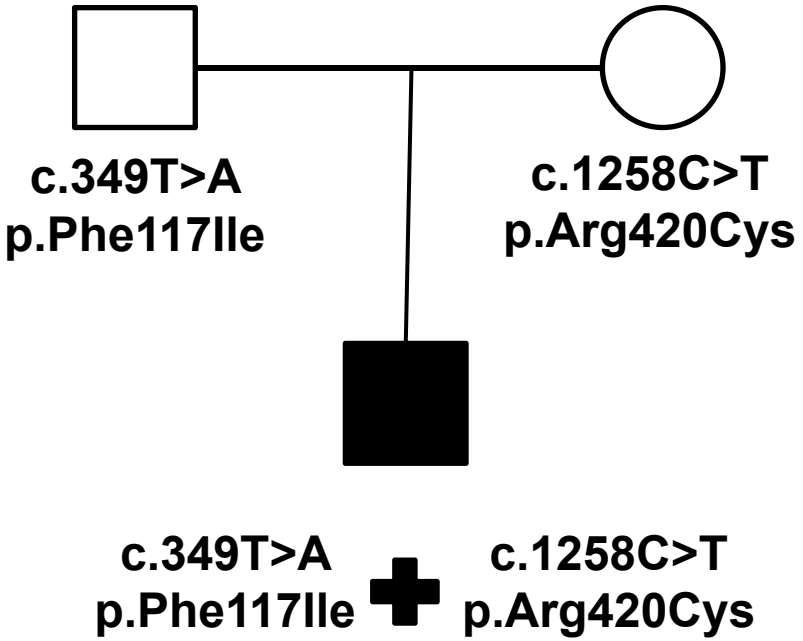
High genetic heterogeneity of Mendelian epilepsies



Autosomal recessive disorders

Early-onset DEE with autosomal recessive inheritance

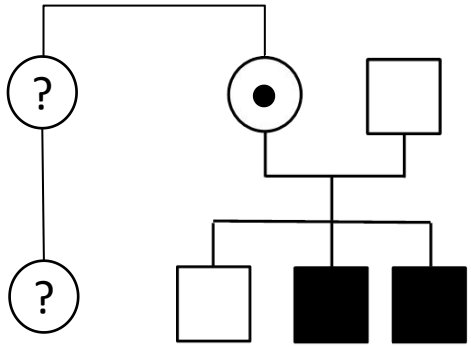
- Multifocal seizures, day 1
- Drug resistant (> 100 seizures/day)
- EEG: migrating partial seizures
- 2 inherited variants in *SLC12A5*
- Encodes the K+/Cl- transporter KCC2
- Functional studies may help to understand the pathological consequences

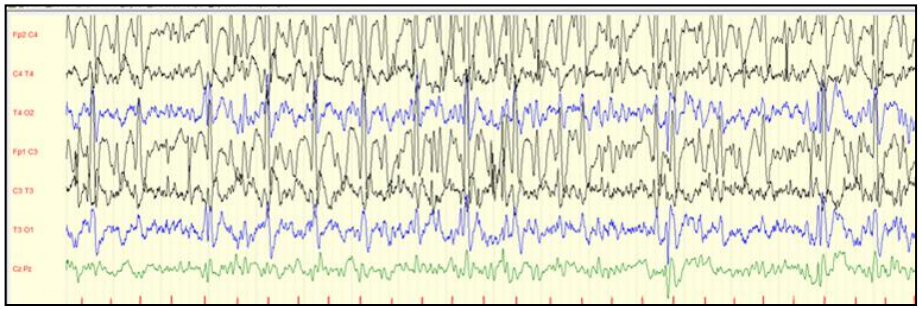


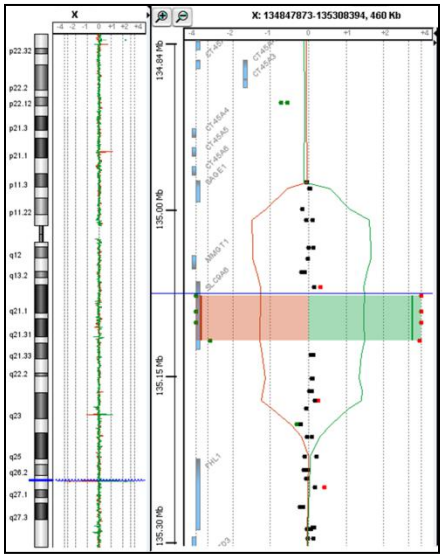
X-linked disorders

X-linked (recessive) epileptic disorders

- Christianson's syndrome with ESES
- Intragenic deletion of *SLC9A6*







X-linked (recessive) epileptic disorders

- Boy with epilepsy and intellectual disability
- No family history
- Normal brain MRI
- No dysmorphic feature
- p.(Ser918Thr) of *CASK*

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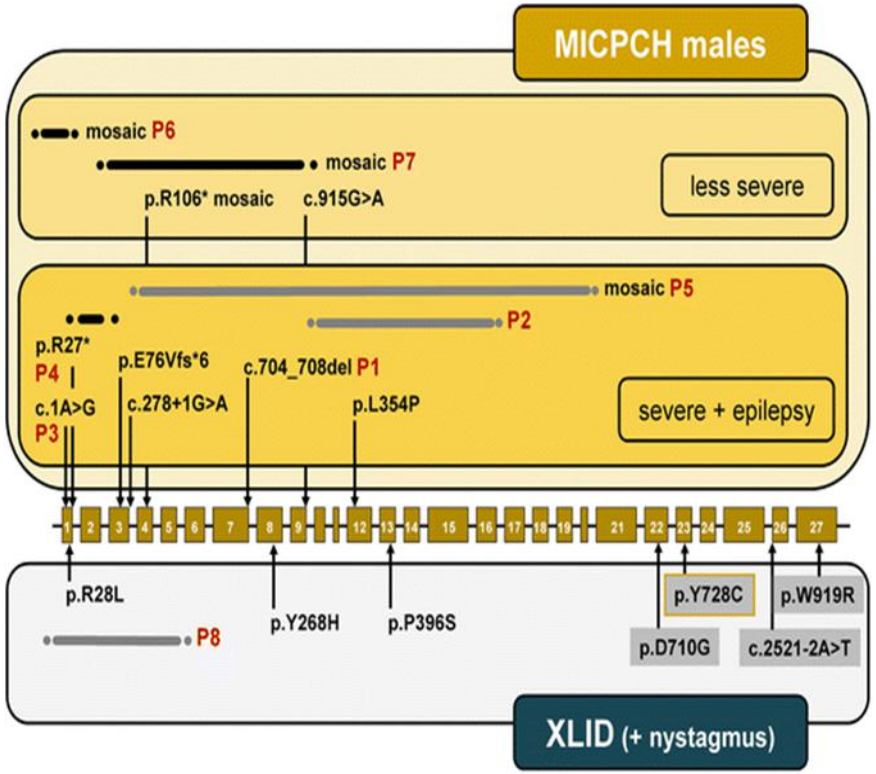

Moog et al., Orphanet J Rare Dis 2015

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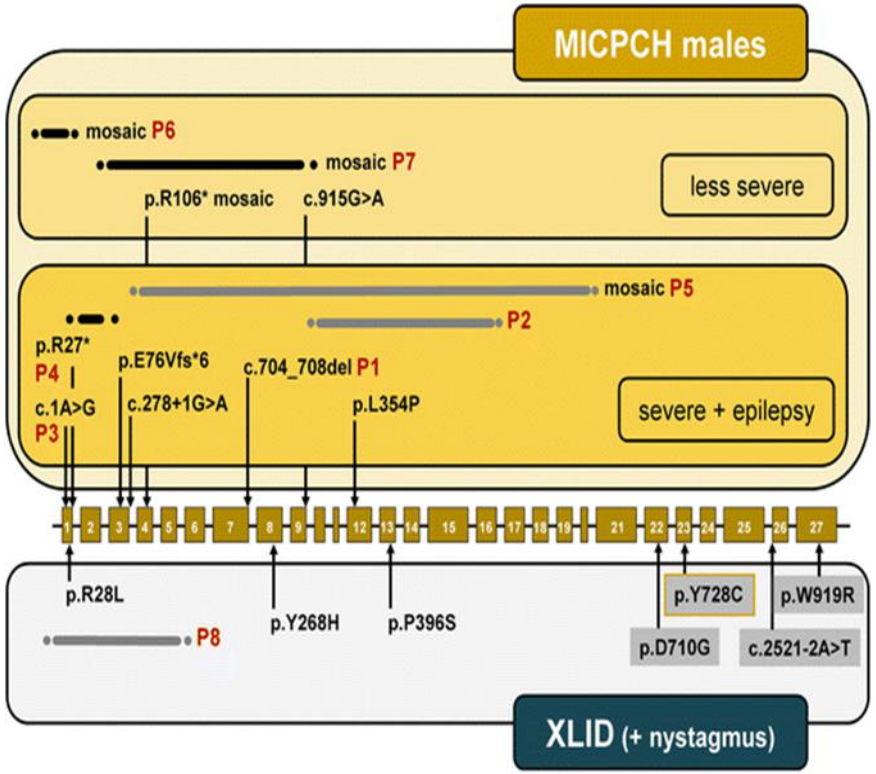

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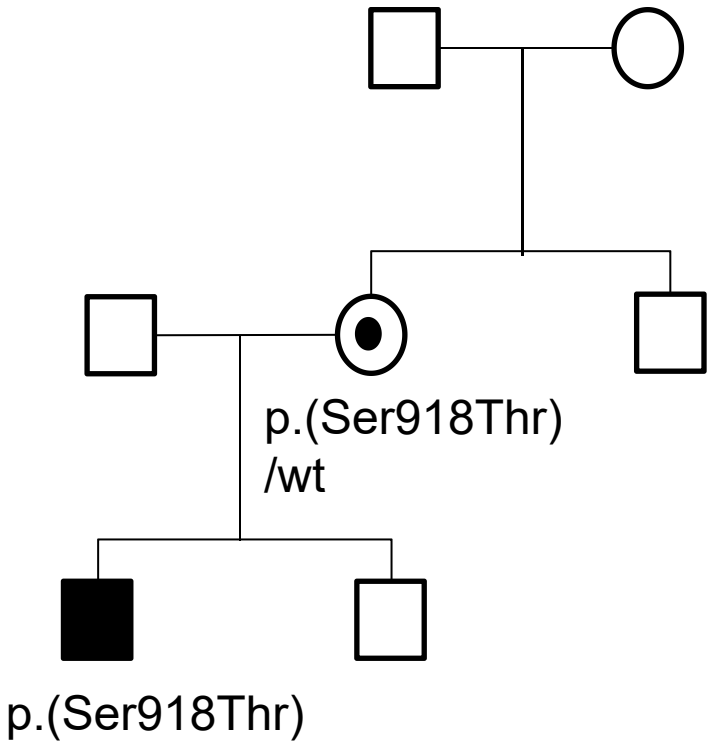
Role in disease ?

Segregation study for X-linked disorders



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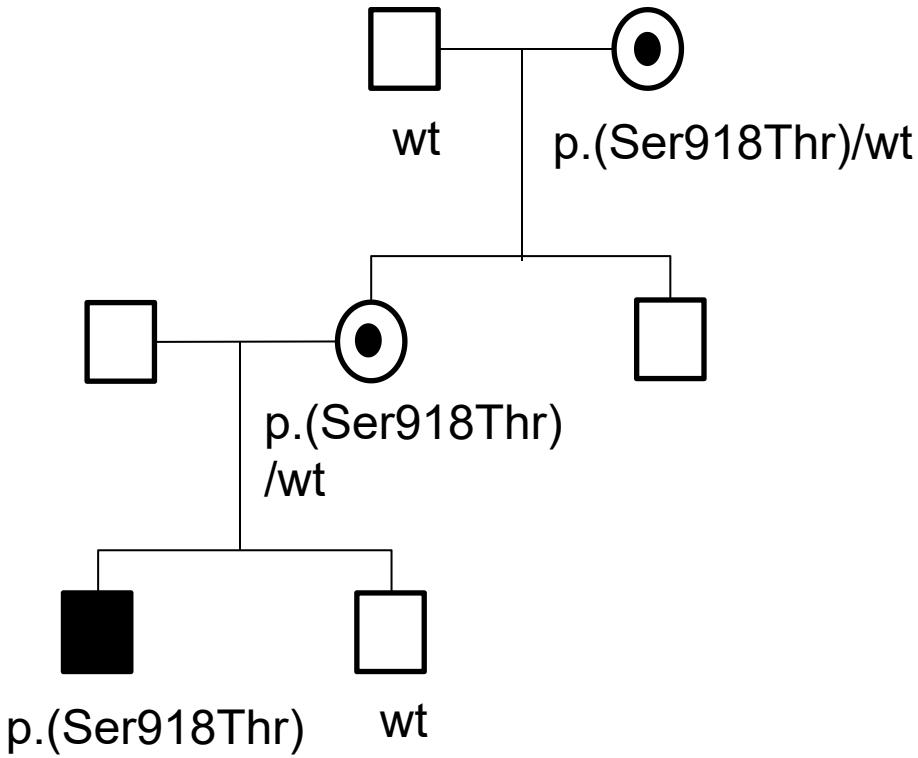

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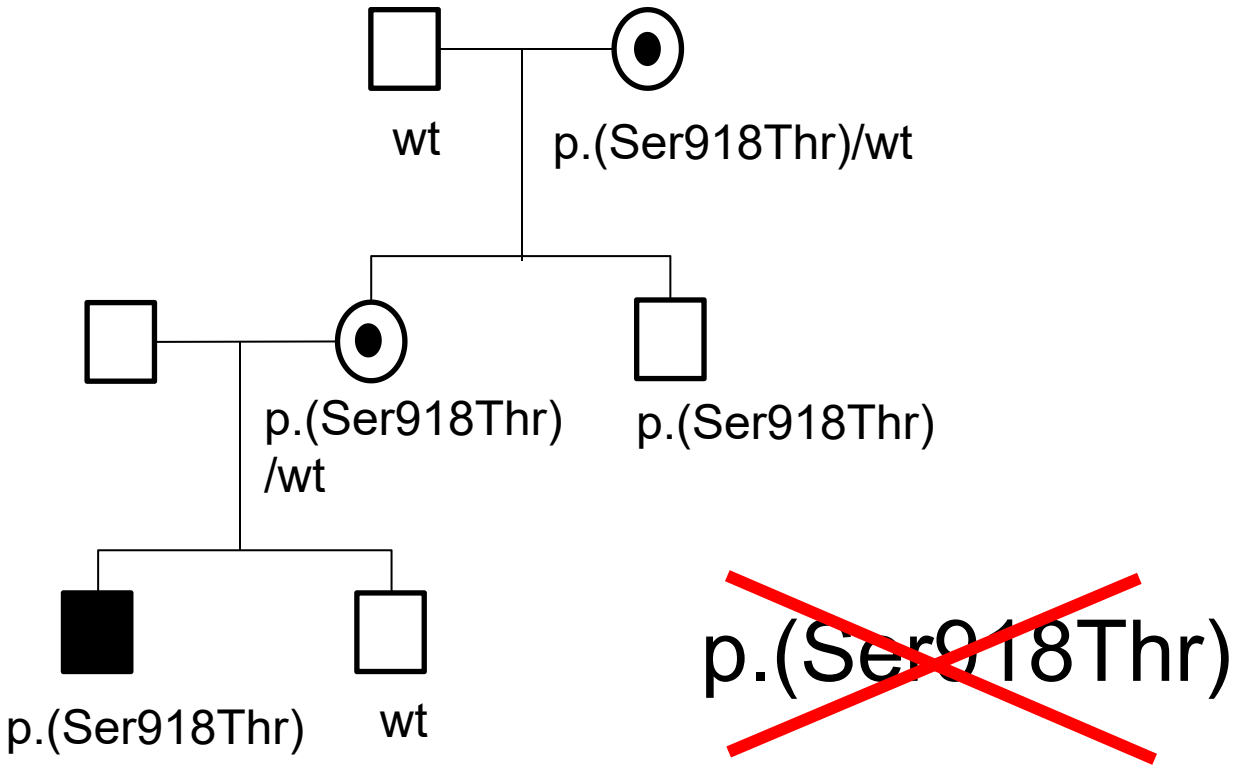
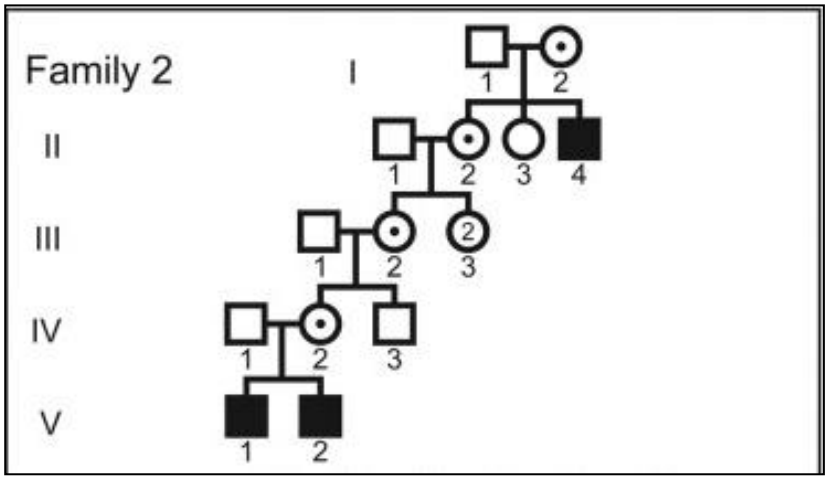


X-linked disorders and variable expressivity in females (*KIAA2022*)

Males

- Inherited loss of function mutations
- Severe intellectual disability, microcephaly, autistic features
- Generalized epilepsy in some



Van Maldergem et al., 2013

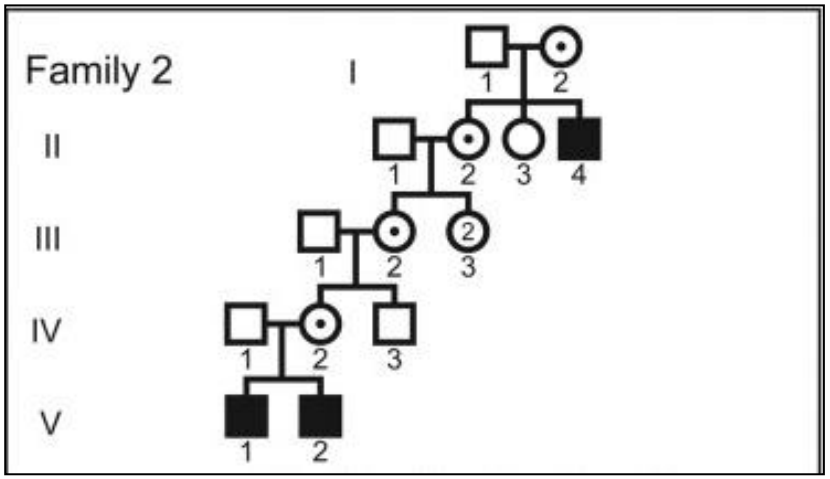
X-linked disorders and variable expressivity in females (*KIAA2022*)

Males

- Inherited loss of function mutations
- Severe intellectual disability, microcephaly, autistic features
- Generalized epilepsy in some

Females

- De novo loss of function mutations
- Mild to severe intellectual deficiency
- **Intractable myoclonic epilepsy**



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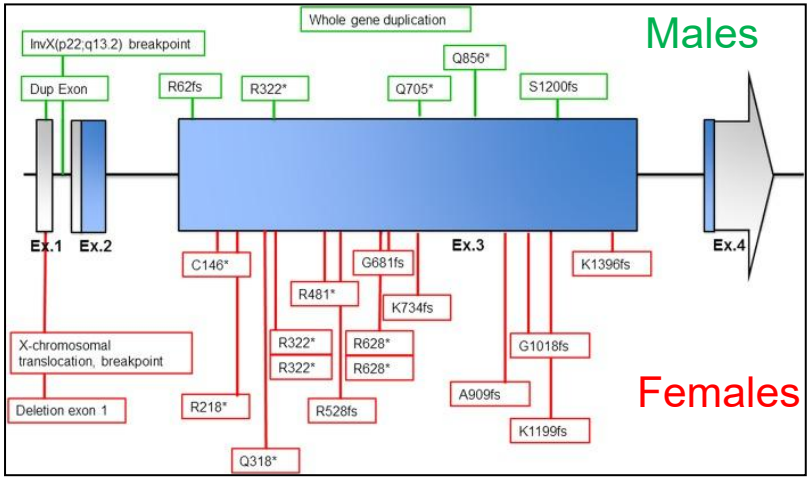
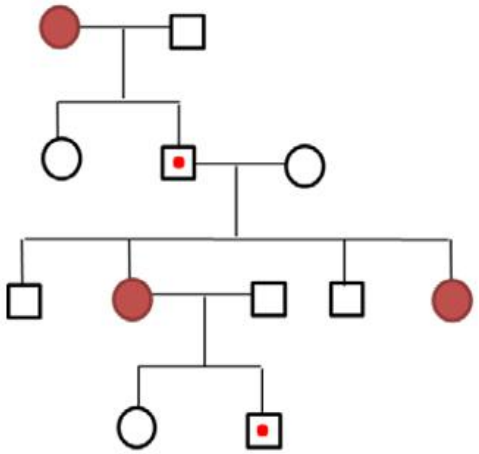
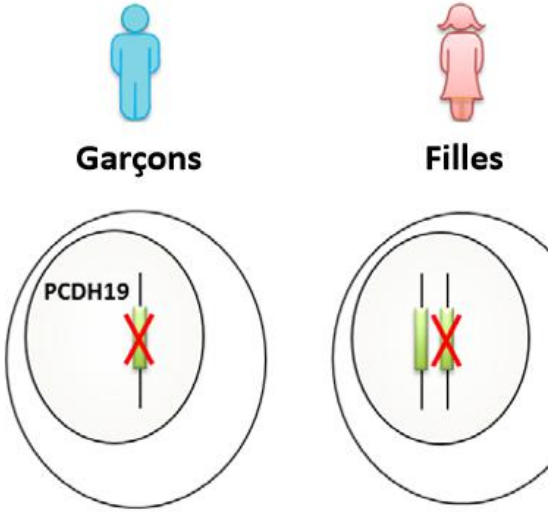


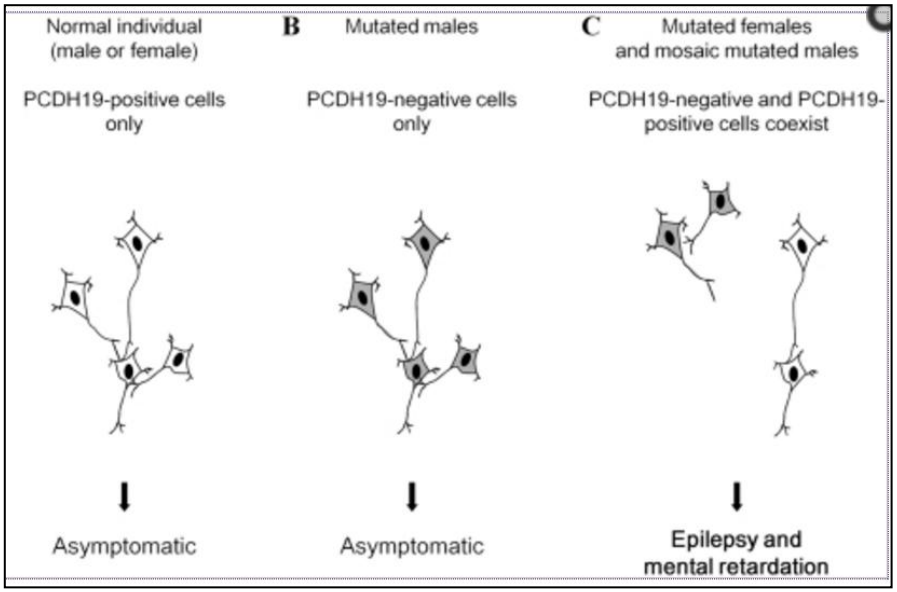
De Lange et al., 2013

PCDH19 and epilepsy in females





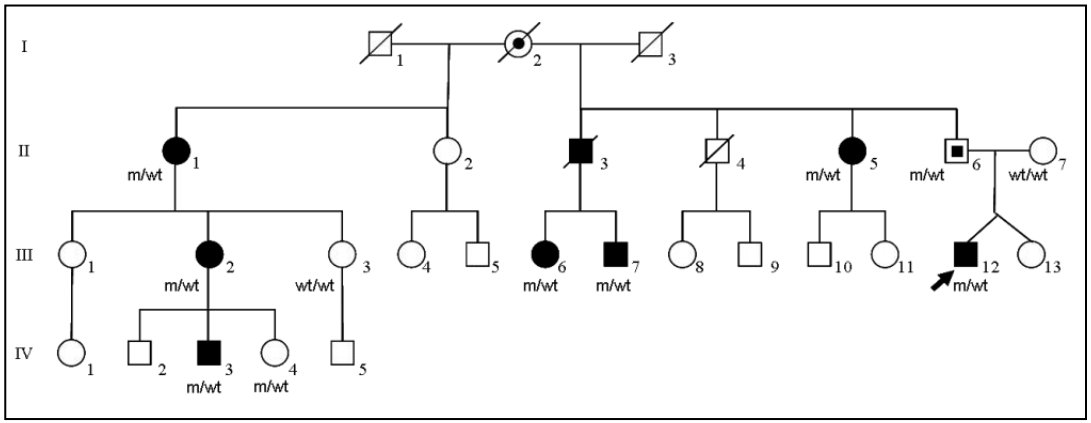
Cellular interference

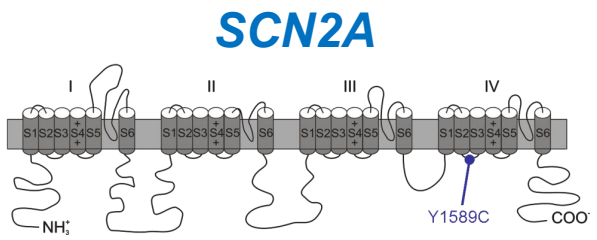


- Female-restricted epilepsy and mental retardation *(Dibbens et al., 2008)*
- Dravet-like syndrome *(Depienne et al., 2009)*

Autosomal dominant disorders

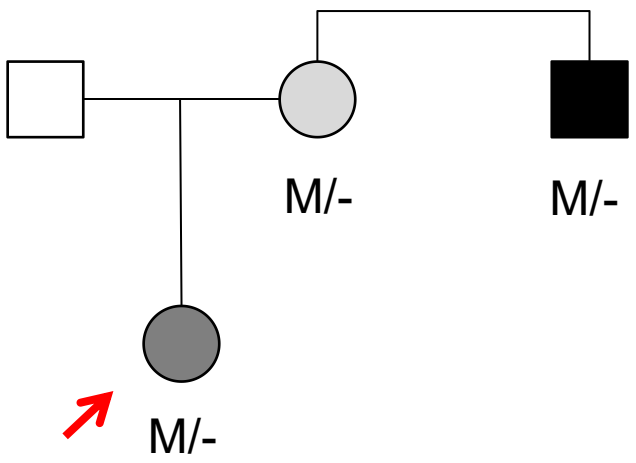
Self-limiting epilepsies in infancy
(Benign familial epilepsies)





			Cognitive impairment
1 day	Benign Familial Neonatal Epilepsy	***KCNQ2*** > *KCNQ3*	**Rare** (5%), **variable severity**
3 months	Benign Familial Neonatal Infantile Epilepsy	***SCN2A***	**No**
1 year	Benign Familial Infantile Epilepsy	***PRRT2***	**No** (only if homozygous)

Genetic febrile seizures plus (GEFS+) and phenotypic variability



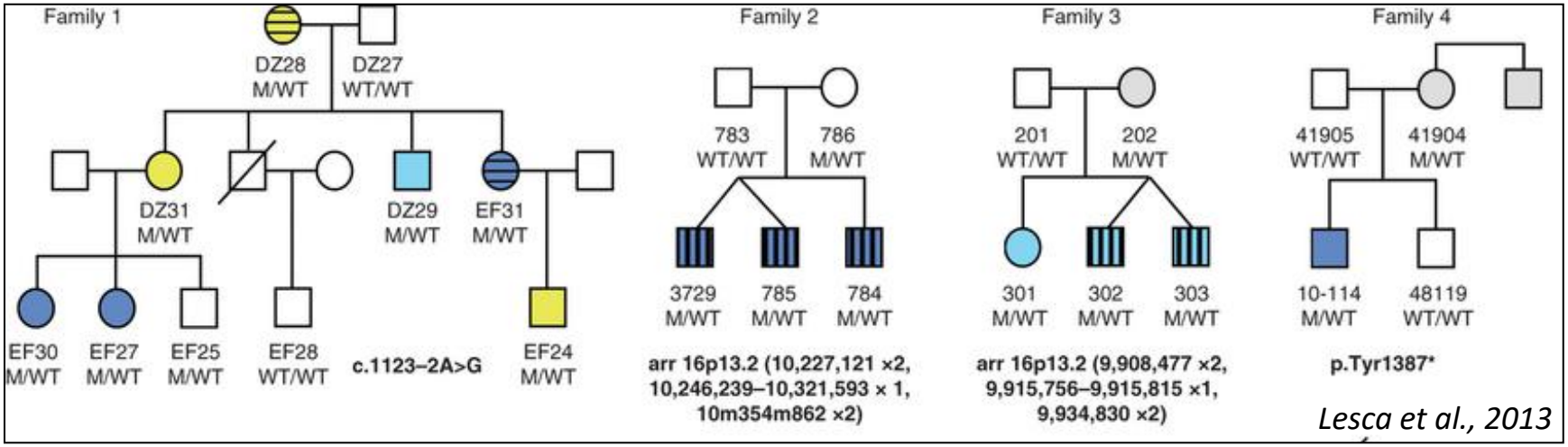
Febrile and non febrile seizures

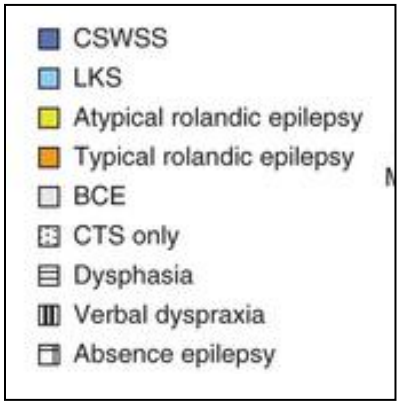
Febrile and non febrile seizures + mild intellectual disability

Dravet syndrome

M Missense variant of *SCN1A*

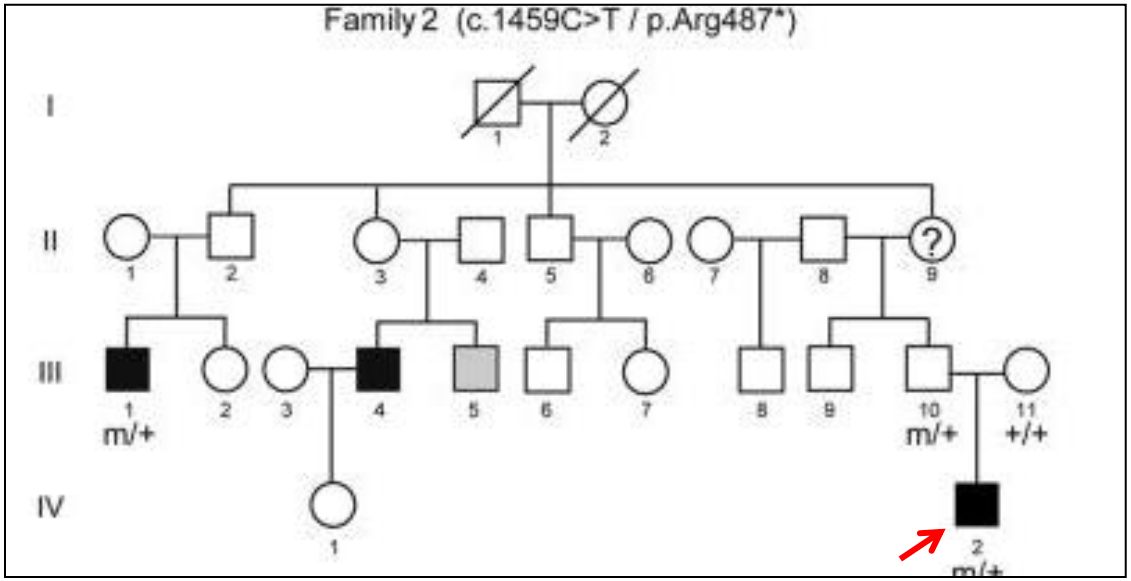
GRIN2A and Landau-Kleffner syndrome / focal epilepsy with CSWS





- High variability of cognitive impairment in patients with LOF variants of *GRIN2A*
- Incomplete penetrance in some individuals (parents)

DEPDC5 focal epilepsy

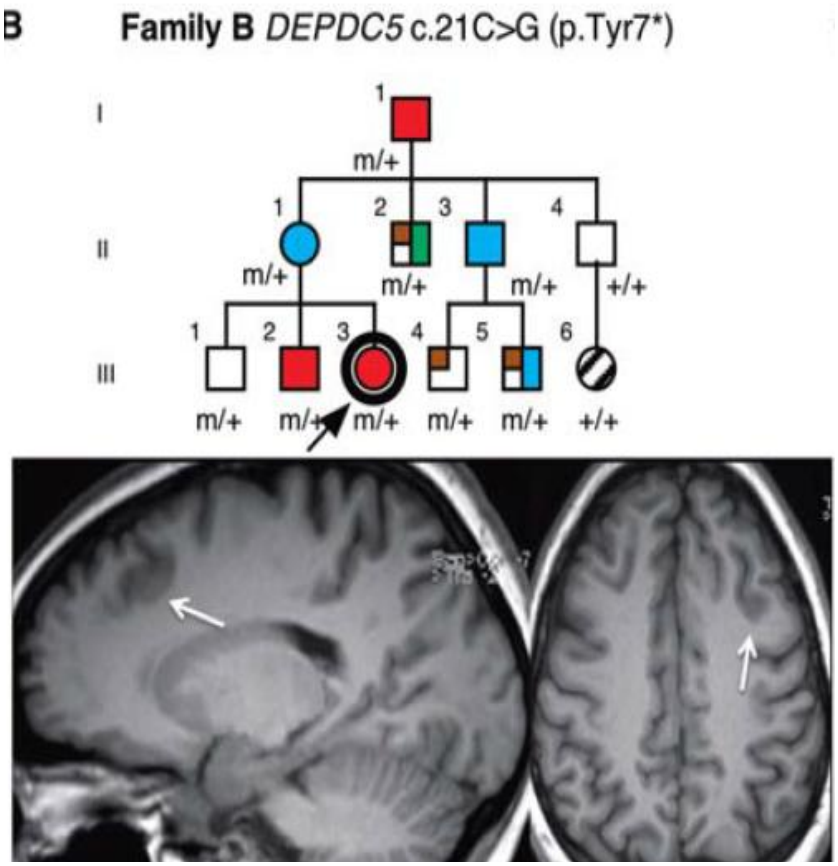


DEPDC5 nonsense variant (stop)

Picard et al., 2014

- Nocturnal > diurnal seizures, since the age of 2
- Several episodes per night, drug resistant
- Incomplete penetrance (50%)

DEPDC5 and lesionnal focal epilepsies



Scheffer et al., 2014

- FCD IIa -> hemimegalencephaly
- 2nd hit = somatic mutation in dysplastic tissue ?
  (Baulac et al., 2015)

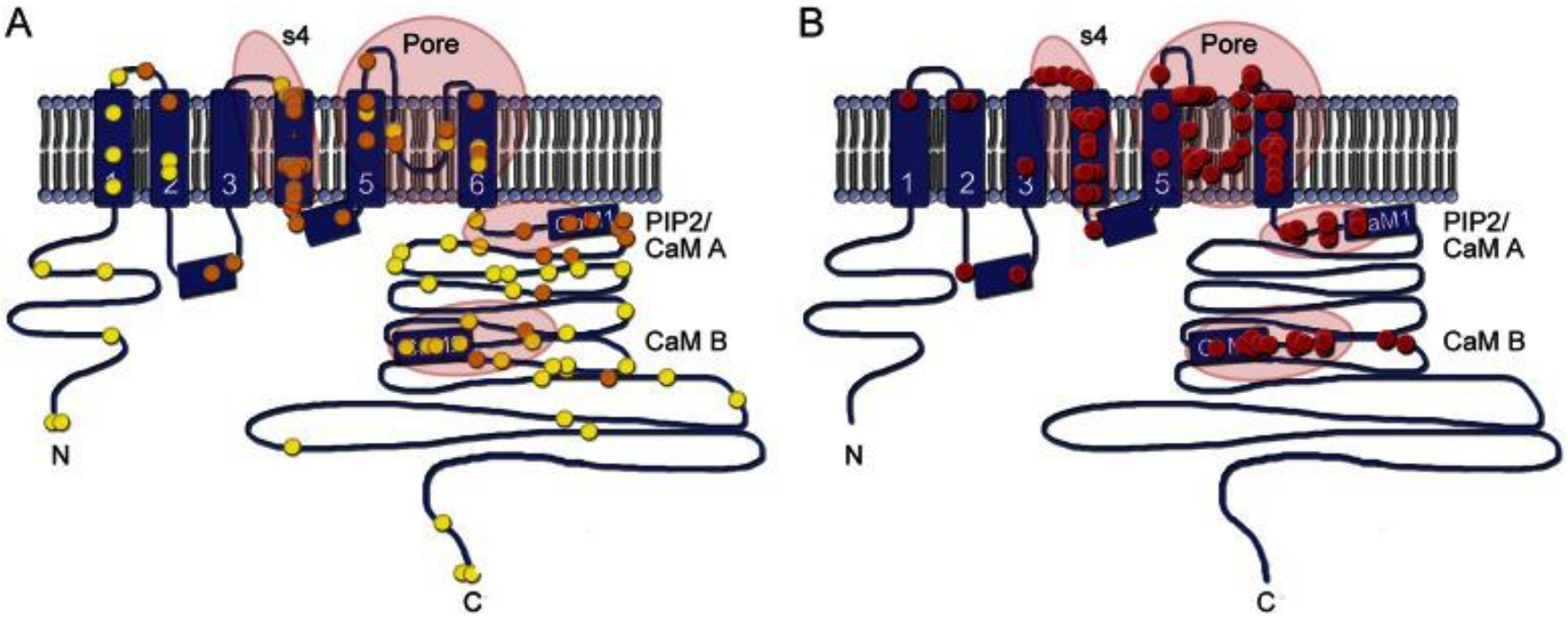
De novo (autosomal dominant) variants

KCNQ2-related epilepsies

(Millichap et al., 2016)

Self-limiting epilepsy (Benin Familial Neonatal Epilepsy)

Early-onset developmental epileptic encephalopathy



Missense variants

Loss-of-function variants

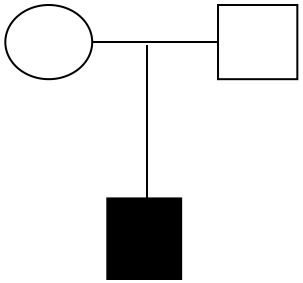
Missense variants

Genes involved in both mild and severe phenotypes

Gene	Mild phenotype (usually inherited)	Severe phenotype (usually de novo)
SCN1A	GEFS+	Dravet syndrome
SCN1B	GEFS+	Dravet syndrome (homozygous mutations)
SCN2A	Benign Familial neonatal-infantile Epilepsy	EOEE
SCN8A	Benign familial infantile epilepsy and paroxysmal choreoathetosis	EOEE
KCNQ2	Benign familial neonatal epilepsy	EOEE
SLC2A1	Refractory generalized or focal epilepsy (early absence epilepsy)	De Vivo syndrome
GABRA1	Idiopathic generalized epilepsy	EOEE
GABRG2	GEFS+	EOEE
GRIN2A	Epilepsy-aphasia syndrome	EOEE

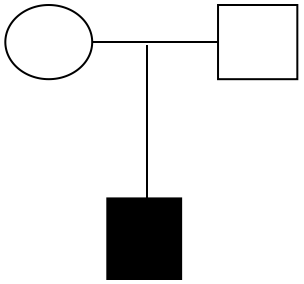
Modified from Helbig and Abou Tayoum, 2016

« Sporadic » cases and genetic risk



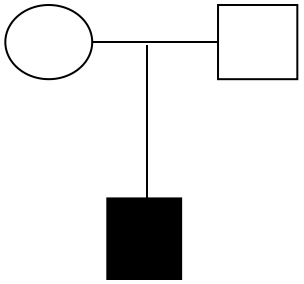
- Any recurrence risk ?

« Sporadic » cases and genetic risk



- *de novo* mutation ?
- X -Linked ?
- Autosomal dominant with incomplete penetrance ?
- Mitochondrial inheritance ?
- Chromosomal inheritance ?

« Sporadic » cases and genetic risk



- *de novo* mutation ?
- X -Linked ?
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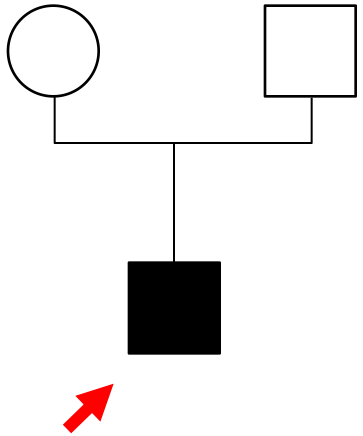
- Mitochondrial inheritance ?
- Chromosomal inheritance ?

The lack of family history does not exclude a Mendelian disorder
… and recurrence risk for the family between 1 and 50%

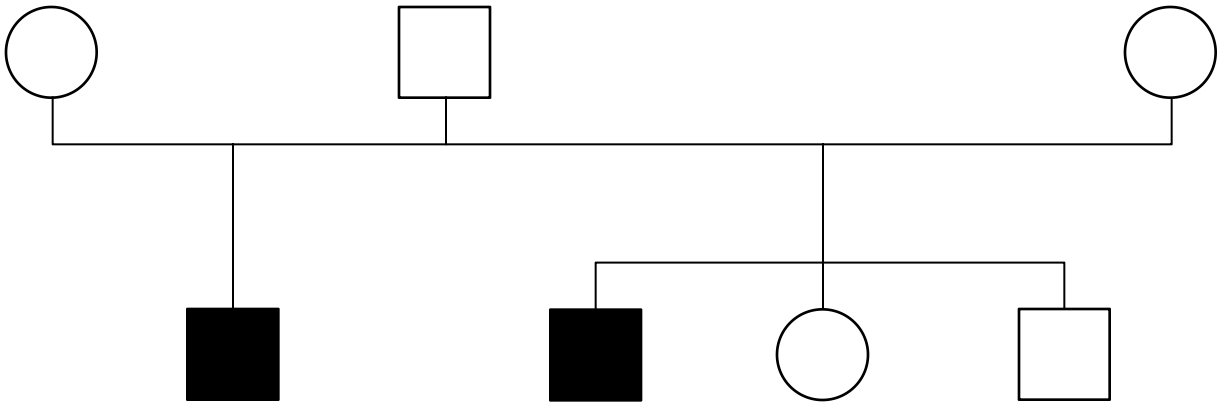
Dravet syndrome

- Onset at 9 months
- Febrile and non febrile seizures
- Drug-resistant epilepsy
- Intellectual disability
- EEG normal at onset, then slowing of background and multifocal anomalies



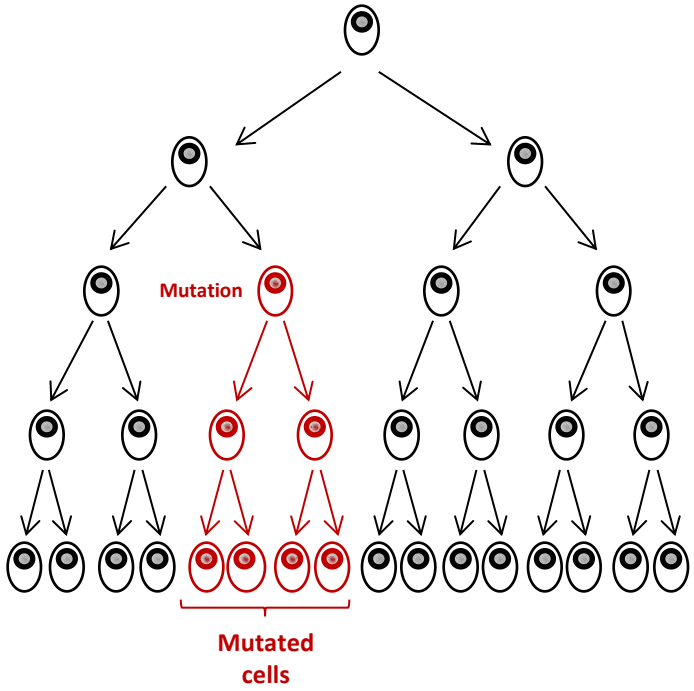
SCN1A pathogenic variant not found in blood-extracted DNA from the parents

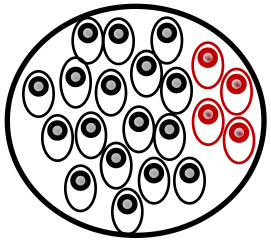
Family recurrence of Dravet syndrome



- Recurrence in a half-brother
- Parental germline/somatic mosaicism in 9% of patients with Dravet syndrome *(Depienne et al., 2011)*

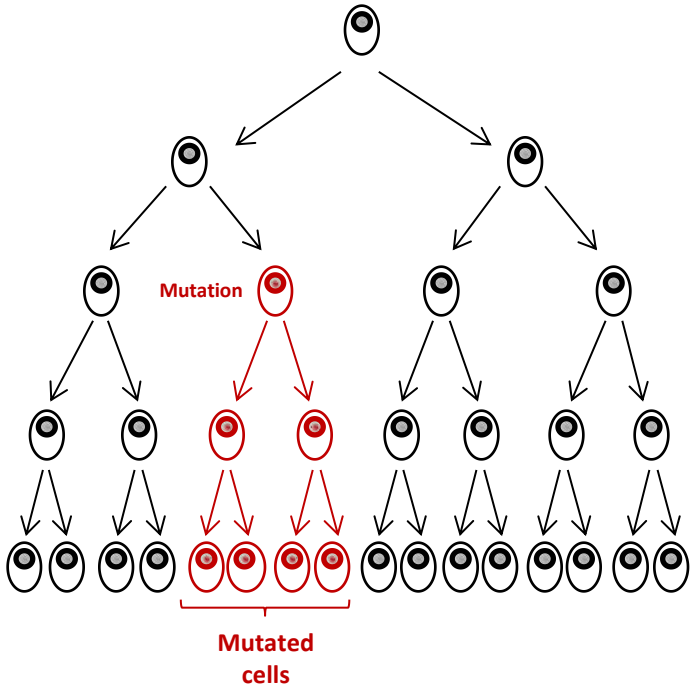
de novo variants and et germline mosaicism

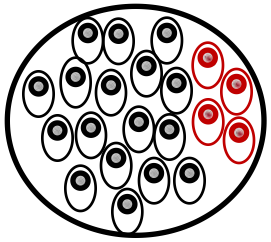




Oocyte / sperm

de novo variants and et germline mosaicism





Oocyte / sperm

- Risk for all *de novo* gene variant or chromosomal anomaly
- PND can be proposed for future pregnancies of the parents (even if separated)

Conclusion

- Should be offered to most families after genetic diagnosis, even when the disease-causing variant had occurred *de novo*
- Mandatory for family planning (prenatal/ premplanation diagnosis) -> when possible before a pregnancy !
- Should be based on acurate genetic diagnosis
- Simple and more complex situations

Thank you for you attention !

Any questions ?

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