Hvordan kan genetikken hjælpe patienter og pårørende til et bedre liv

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Epilepsikonferencen, 2024

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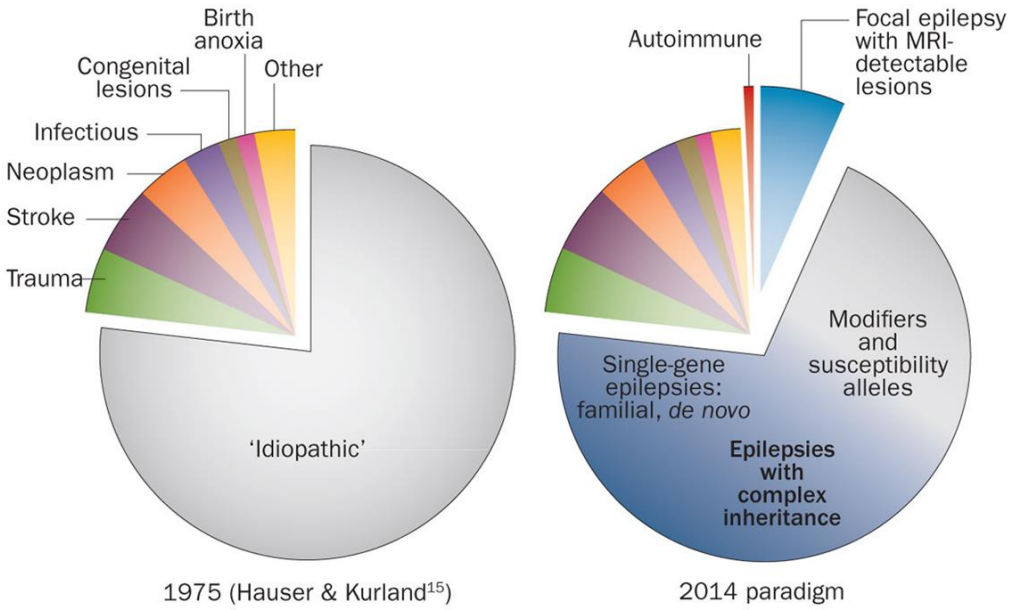
EPILEPSI FORENINGEN

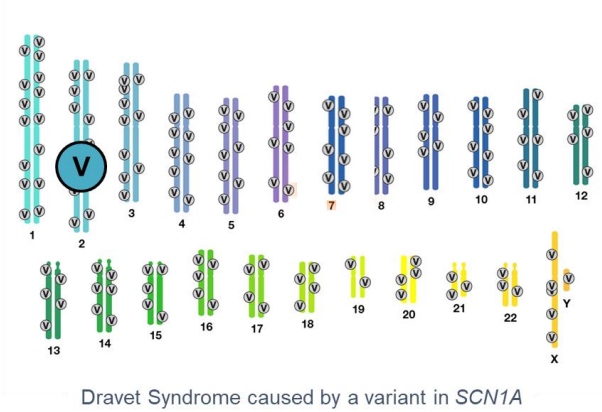
FILADELFIA

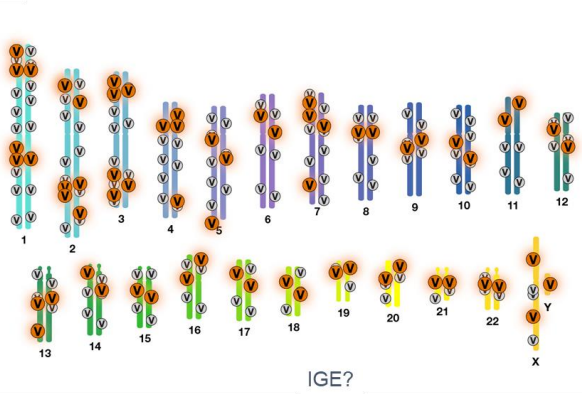
Epilepsi er ikke én sygdom - ætiologi



Thomas and Berkovic, 2014

Monogene versus polygene sygdomme





https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

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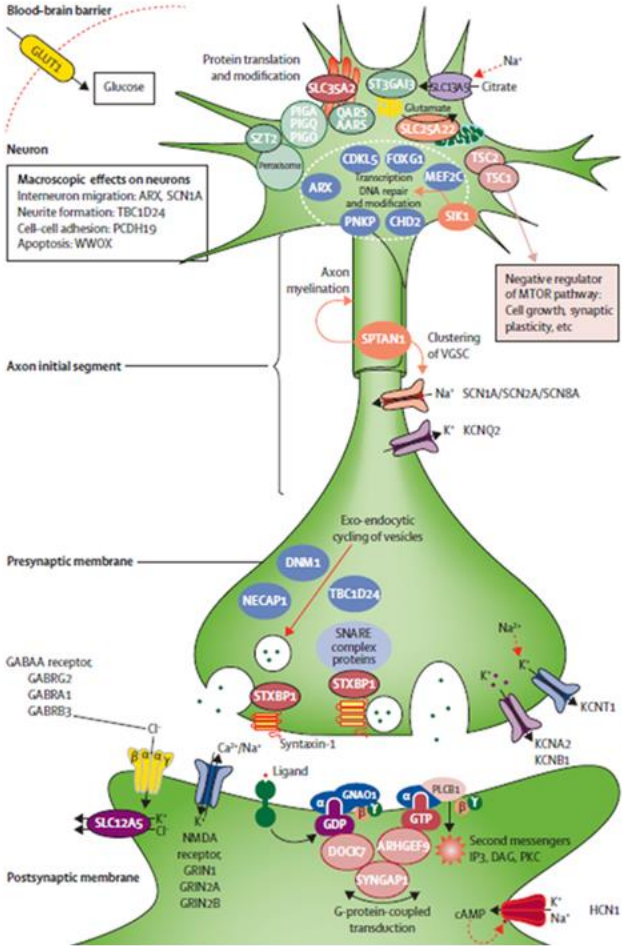
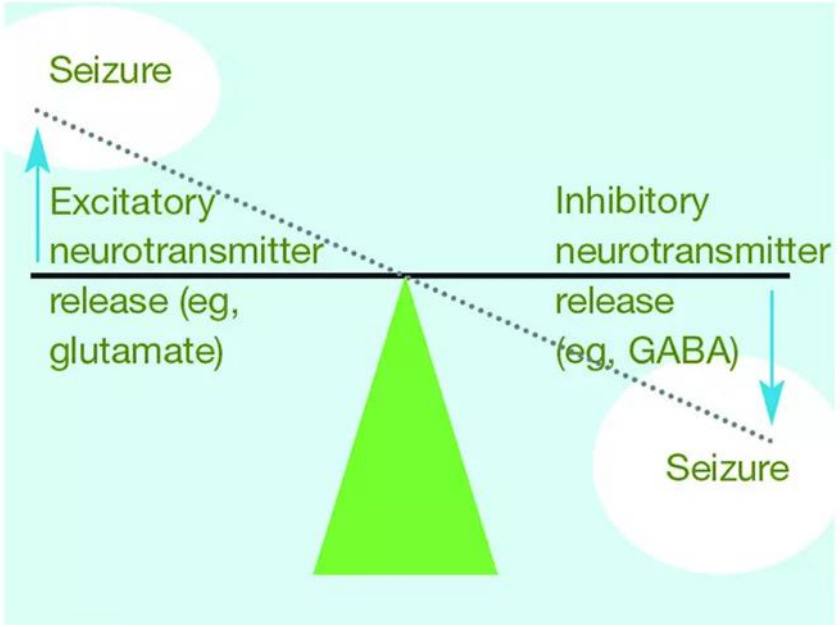
FILADELFIA

Epilepsigenetik – hvad ved vi i 2024?

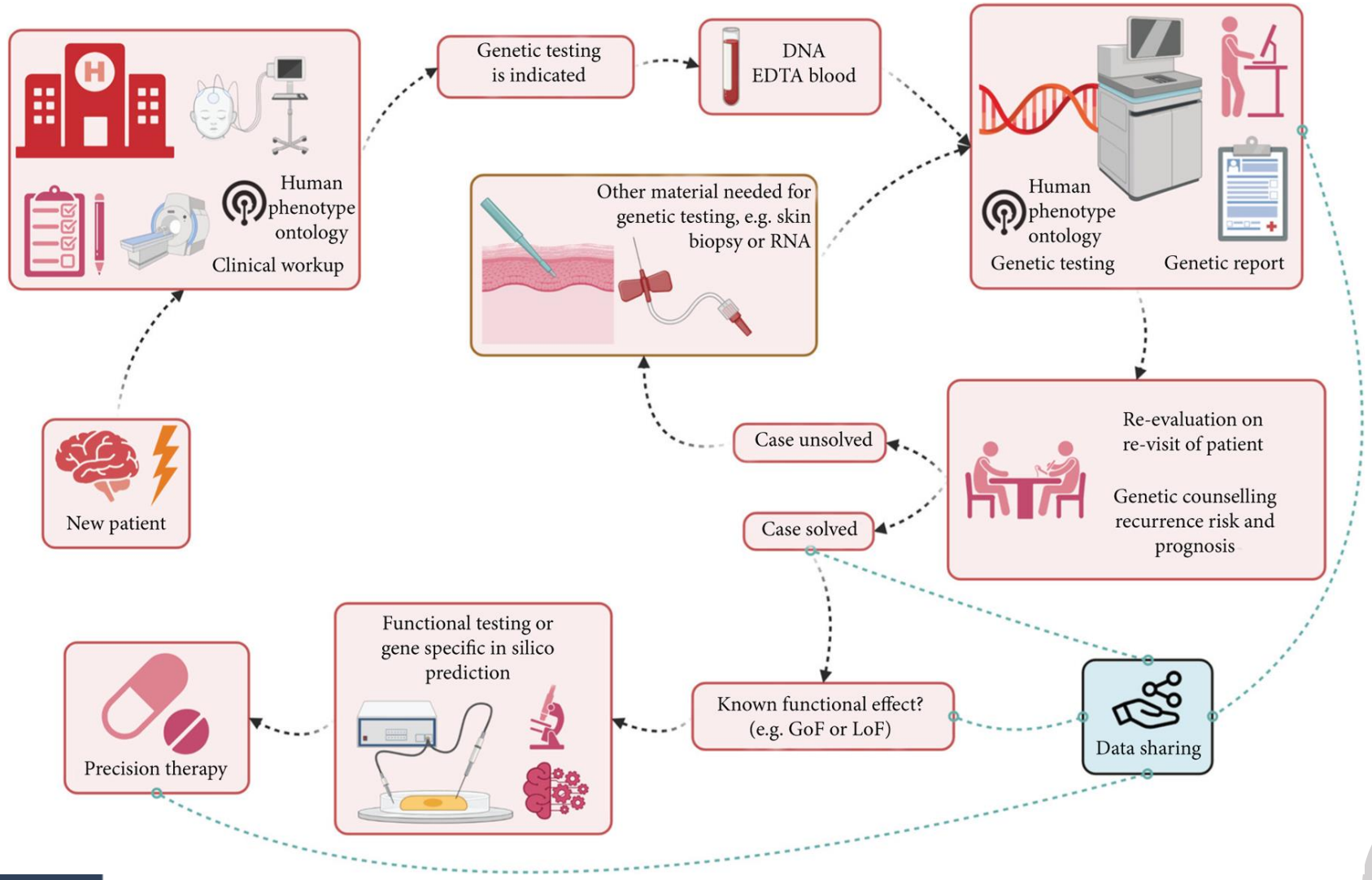


McTague et al, 2016



https://pharmaceutical-journal.com/article/ld/epilepsy-review-what-you-know-part-1

Workflow for genetisk udredning ved epilepsi



Krey I, *et al.* Epileptic Disorders 2022;24:765–86;

Hvornår skal genetisk testing overvejes?

Genetisk testning er anbefalet anbefalet ved[1]:

- Tidligt indsættende epilepsi (<4år): (EI)DEEs, SeLNE, SeLFNIE, SeLIE
- Epilepsi + udviklingshæmning, autisme eller anden komorbiditet
- Progressive myoklone epilepsier
- Specifikke familiære fokale epilepsisyndromer: ADSHE, ADEAF

Genetisk testning bør overvejes ved[1] :

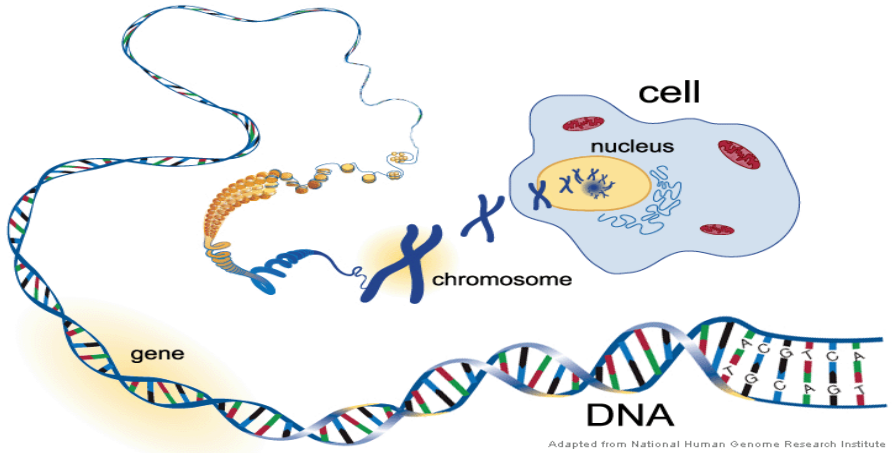
- MR-negative behandlingsrefraktære fokale epilepsier som led i kirurgiudredning
- Epilepsi som følge af strukturelle hjernemisdannelser

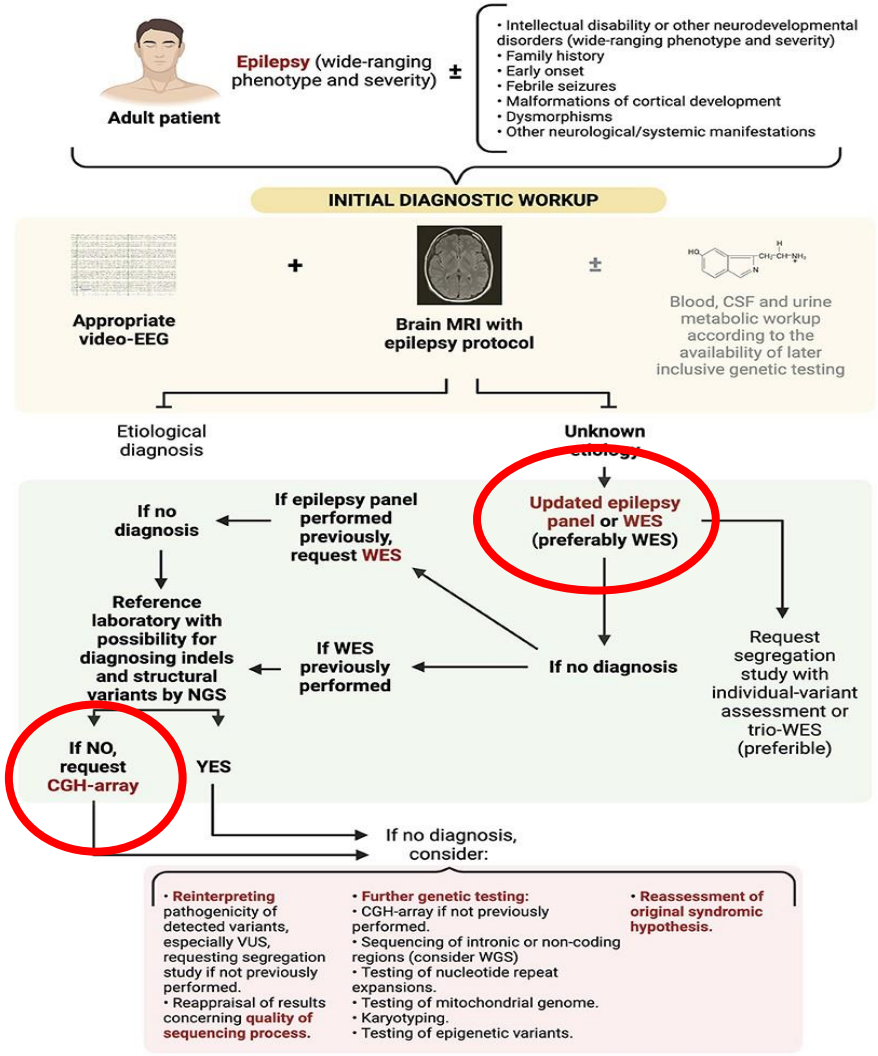
ADSHE, autosomal dominant sleep related hypermotor epilepsy; ADEAF, autosomal dominant epilepsy with auditory features; CGH, comparative genomic hybridization; CSF, cerebrospinal fluid; (EI)DEE, (early infantile) developmental and epileptic encephalopathies; EEG, electroencephalography; MRI, magnetic resonance imaging; NGS, next generation sequencing; SeLIE, self-limited infantile epilepsy; SeLFNIE, self-limited familial neonatal-infantile epilepsy; SeLNE, self-limited neonatal epilepsy; VUS, variants of uncertainty significance; WES, whole exome sequencing; WGS, whole genome sequencing.

Krey I, *et al.* Epileptic Disorders 2022;24:765–86;

Den humane arvemasse og testningsmetoder

- 46 kromosomer, 3.000 millioner baser
- Kodende DNA dvs. gener: 1-2 %
- Gener:
  - 20.000 gener
  - 7.000 er sygdomsrelaterede
  - 800 kan give epilepsi
  - 50% uden kendt funktion





Beltrán-Corbellini Á, *et al.* Front Neurol 2022;13

Genetisk udredning – hvad kan man forvente?

29.0%

Infancy
(0-1 years)
(n = 162)

13.6%

Early childhood
(2-4 years)
(n = 88)

7.0%

Late childhood
(5-10 years)
(n = 143)

2.4%

Adolescence
(11 – 17 years)
(n = 210)

3.7%

Adulthood
(18+ years)
(n = 162)

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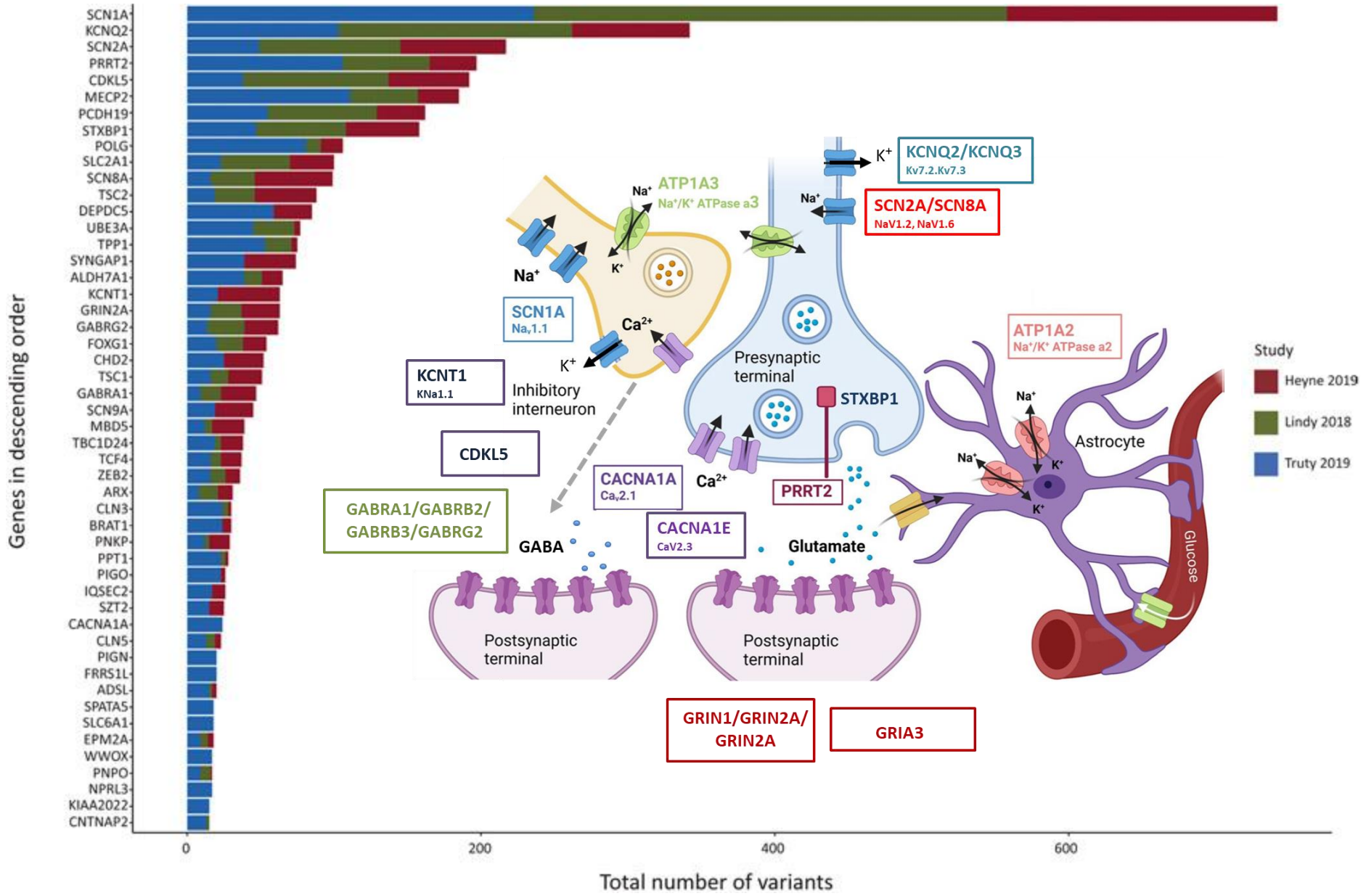
McKnight D et al Neurol Genet 2021 Dec 16;8(1) e650

FILADELFIA



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Knowles J, et al. Epilepsia, 2022: 2461-2475

Modified from Grangeon et al, The journal of headache and pain, 2023; 24:12

Genetisk udredning – hvad kan man forvente?

- Progressive myoklone epilepsier: 70% (~30 gener; *CSTB, EPM2A, NHLRC1*)
- Epileptiske encefalopatier: 30-40% (~300 gener; *SCN1A, STXBP1, CDKL5*)
- Familiære fokale epilepsier: 30-90% (~40 gener; *PRRT2, KCNQ2, SCN2A*)
- Isolerede fokale epilepsier 5-10% (~40 gener; *DEPDC5, NPRL2/3, SCN1A*)
- Idiopatisk/genetisk generaliserede epilepsier: 3% (~5 gener; *GABRA1, SLC2A1*)

Gentagelsesrisikoen for førstegradsslægtninge til personer med isoleret fokal epilepsi eller IGE/GGE

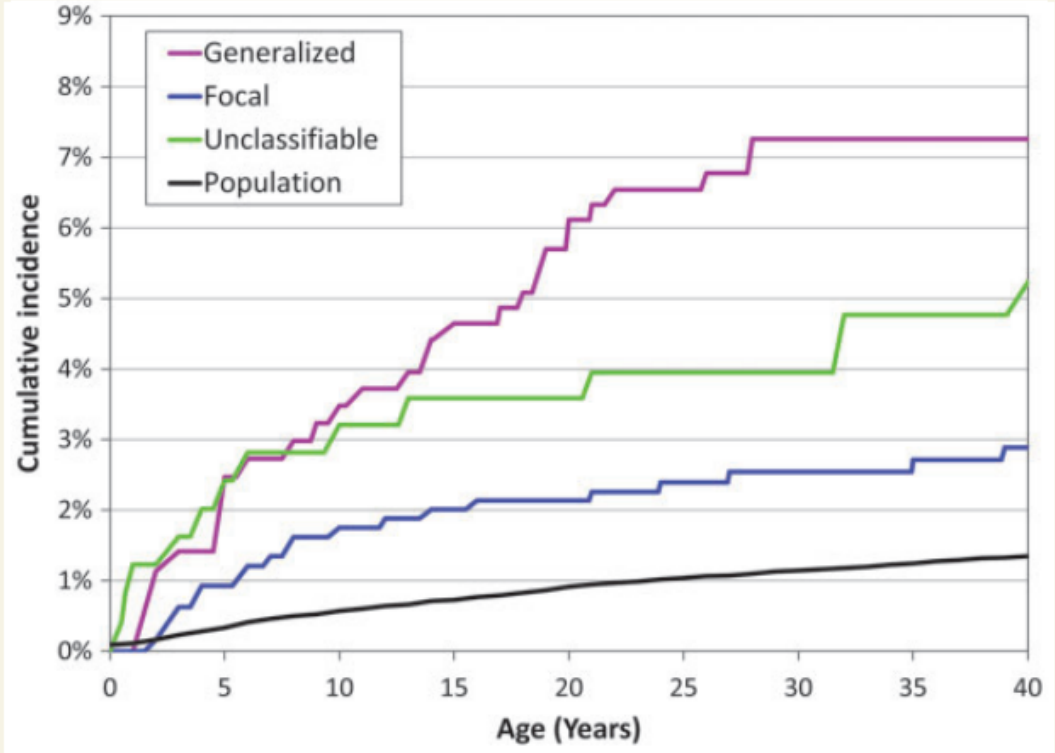
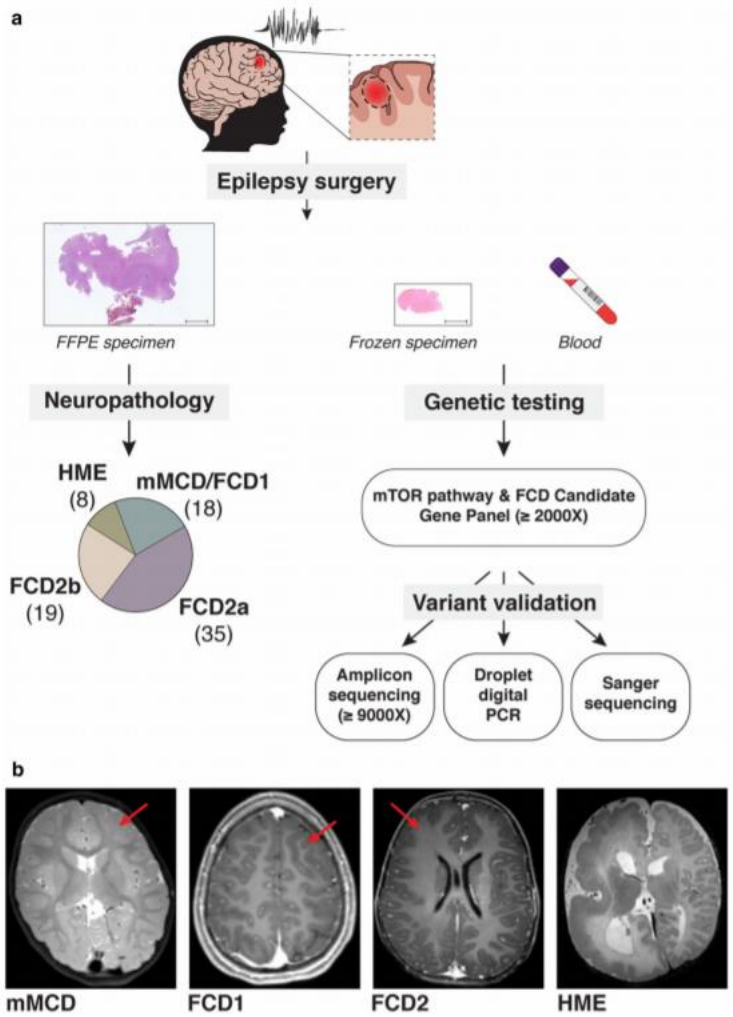


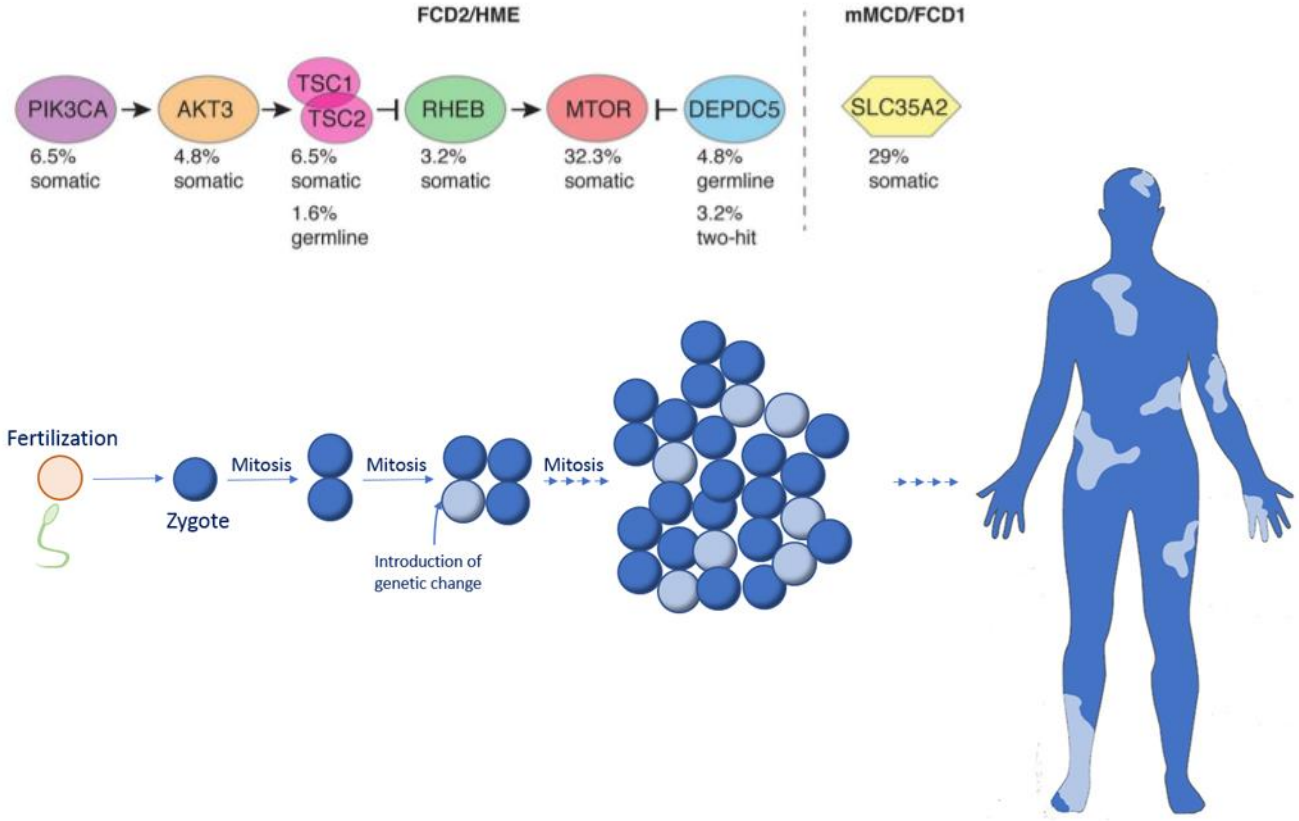
Figure 1 Age-specific cumulative incidence of epilepsy in first-degree relatives of probands with epilepsy, by proband epilepsy type.

Peljto AL, Brain. 2014 Mar;137(Pt 3):795-805

Testning af blod er ikke altid nok - Somatiske varianter i strukturelle hjernemisdannelser

~30%: mMCD/FCD1 og ~60%: FCD2/HME





Acta Neuropathol. 2019 Aug 23. doi: 10.1007/s00401-019-02061-5. [Epub ahead of print]

Dissecting the genetic basis of focal cortical dysplasia: a large cohort study.

Baldassari S[1,2,3,4], Ribierre T[1,2,3,4], Marsan E[1,2,3,4], Adle-Biassette H[5,6,7], Ferrand-Sorbets S[8], Bulteau C[8], Dorison N[8], Fohlen M[8], Polivka M[7], Weckhuysen S[1,2,3,4,9], Dorfmüller G[8], Chipaux M[8], Baulac S[10,11,12,13].

Neurol Genet. 2016 Oct 31;2(6):e118. eCollection 2016 Dec.

Germline and somatic mutations in the *MTOR* gene in focal cortical dysplasia and epilepsy.

Møller RS[1], Weckhuysen S[1], Chipaux M[1], Marsan E[1], Taly V[1], Bebin EM[1], Hiatt SM[1], Prokop JW[1], Bowling KM[1], Mei D[1], Conti V[1], de la Grange P[1], Ferrand-Sorbets S[1], Dorfmüller G[1], Lambrecq V[1], Larsen LH[1], Lequern E[1], Guerrini R[1], Rubboli G[1], Cooper GM[1], Baulac S[1].

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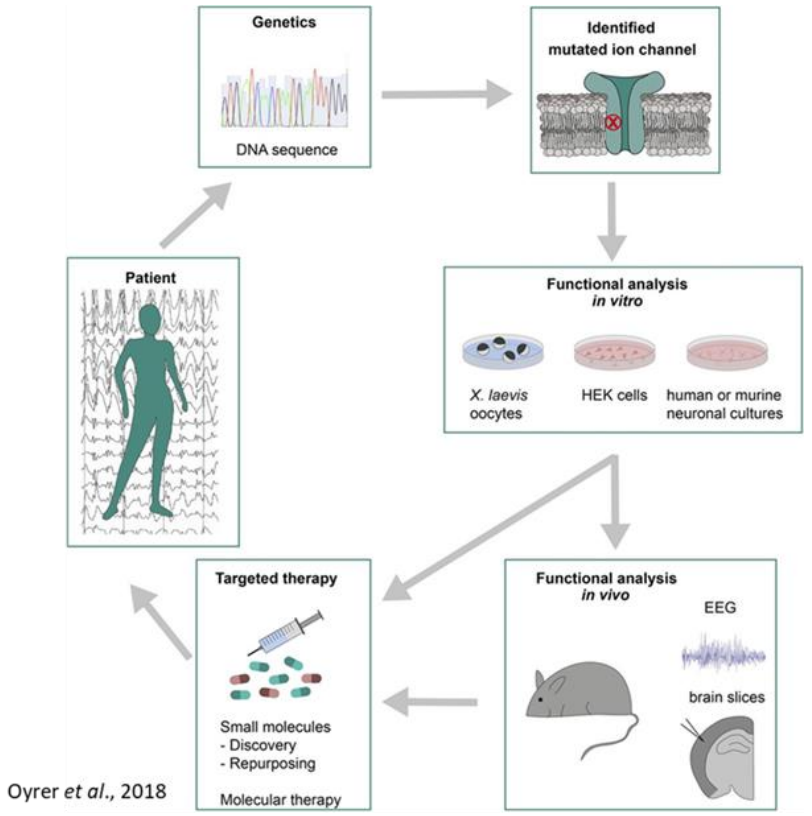
Hvorfor skal man lave genetisk testning

- Kan give vished
- Prognose
- Familieplanlægning
- Møde ligesindede – få et netværk
- Guide behandling



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FILADELFIA

dravet danmark

Forside | Kort om Dravet Syndrom | Råd og Vejledning | Nyheder | Hvem er vi? | Kontakt os | Støt

Velkommen til Dravet Danmark

Dravet Danmark blev dannet den 10. marts 2019, som en "diagnosegruppe" under Epilepsiforeningen.

Vores mission er:

1. Udbrede viden om og kendskab til Dravet syndrom til pårørende, myndigheder og offentligheden generelt.
2. Fremme initiativer og tilbud, der støtter mennesker o og support.
3. Samarbejde med andre relevante foreninger samt eks
4. Arbejde for at sikre bedre behandling og tidligere dia adgang til behandlingstilbud, herunder også adgang
5. Fremme viden om og forskning i Dravet og livet med

kcna2epilepsy.org/kcna2-epilepsy/our-stories-

KCNA2

Epilepsy Sparks

Facts and glossary | Research | Merch | Podcast | YouTube | Organisations | About us

CURE GABA A VARIANTS

GABA ALLIANCE

Bridging the gap between patients, neurologists, and scientists

Making learning about epilepsy cool

Move to Cure STXBP1 Disorders

SynGAP Research Fund

Collaboration. Transparency. Urgency.

SNA

We're called The Cute Syndrome Foundation for a reason.

KCNT1 EPILEPSY

HOPE IS ON THE HORIZON

SLC6A1 Connect

SLC6A1 Research & Support

AMELAS TÆTTESTE VENNER ER UDENLANDSKE MØDRE TIL BØRN MED SAMME SJÆLDNE GENFEJL SOM AMELAS SØN

> Amela H. Topic og hendes mand, Mustafa Topic, manglede desperat svar og kontakt til ligesindede, da deres søn Arian for 7 år siden fik en ekstremt sjælden genetisk diagnose. Der var ingen hjælp at hente, så Amela måtte selv handle.

EPICARE – det europæiske referencenetværk for sjældne og komplekse epilepsier

Rare epilepsies leaflets

Patient and caregivers leaflets are developed to give precise and accessible informations on rare and complex epilepsies. With **one part for healthcare profesionnals, and one part for patients and their families or carers**, these documents detail comprehensively what to expect when facing a rare epilepsy, and how to manage care.

Unless mentioned otherwise, all leaflets are in english. We are working on translating them in as many languages as possible with the help of patients associations all over Europe, so check back regularly!

Read and download the following leaflets:

- **Dravet** Syndrome leaflet (EN) / Dravet versione italiana (IT) / Dravet Versiunea română (RO) / Dravet hrvatska verzija (HR) / Dravet deutsche Version (DE) / Dravet Norsk versjon (NO) / Dravet srpska verzija (RS) / Dravet Svensk version (SE)
- **Hypothalamic Hamartoma** leaflet / Hypothalamic Hamartoma Versiunea română (RO) / Hypothalamic Hamartoma Hrvatska verzija (HR)
- **Ring Chromosome 20** leaflet / Ring Chromosome 20 Hrvatska verzija (HR) / R(20) ελληνική έκδοση (GR) / R(20) Lietuviška versija
- **Alternating Hemiplegia of Childhood** leaflet (EN) / AHC Hrvatska verzija (HR) / AHC Versione italiana (IT) / HAI Versión española / Version française (FR)
- **GLUT1 Deficiency Syndrome** leaflet (EN) / GLUT1 Hrvatska verzija (HR) / GLUT1 Versiunea română (RO) / Glut1 Deutsche Version (DE) / Glut1 versione italiana (IT)
- **CDKL5 Deficiency Disorder** leaflet (EN) / CDKL5 Versión española (ES) / CDKL5 Versão portuguesa (PO) / CDKL5 Hrvatska verzija (HR) / CDKL5 Versiunea română (RO)
- **Lennox-Gastaut syndrome** leaflet (EN) / Lennox-Gastaut syndrome Versiunea română (RO) / Lennox-Gastaut Hrvatska verzija (HR)
- **SYNGAP1** leaflet (EN) / SYNGAP1 Versiunea română (RO) / SYNGAP1 Hrvatska verzija (HR)
- **RETT** Syndrome leaflet (EN) / RETT Hrvatska verzija (HR)
- **Infantile Epileptic Spasms Syndrome** leaflet (EN) / IESS Hrvatska verzija (HR)
- **STXBP1** leaflet (EN) / STXBP1 Hrvatska verzija (HR)

These documents are being developed progressively. New ones should be added soon.

Patient journey KCNQ2-encephalopathy

EpiCARE

1 ….first symptoms…. 2 ….diagnosis…. 3 ….treatment….. 4 …follow up… 5 ….transition…

1. FIRST SYMPTOMS

Timeline: from the 1st day of life up to 1 year

Clinical signs / Symptoms
- In most cases neonatal seizures occur in the first days of life.
- In some cases, the seizures present after 1 month and within the first year of life.
- Epilepsy may be absent; in few cases, despite no signs of seizures, an abnormal eeg accompanies delays in development and or behavioral development.

Identify patient needs
- Parents need to be correctly informed about how different forms of seizures need to be managed.
- Parents need to have basic information on epilepsy and epileptic seizures
- Parents need to be informed their child could have a severe cognitive disability
- Parents need to know how to access early rehabilitation

Ideal results/ Support
- Parents concerns are taken seriously and are given reassurance.
- Families are given instructions on how to manage an epileptic attack should it recur; description of emergency medication and when to go to hospital
- Rehabilitation plan

2. DIAGNOSIS

Timeline: from 2 months up to 6 years (normally at 2 years)

Clinical signs / Symptoms
- Developmental progress differs from child to child, this disease effects the entire lifespan of the person
- Even in the first few months overall development is delayed; people affected by a KCNQ2 encephalopathy rarely become independent
- The child has several different types of epileptic seizures: focal or generalized seizures, tonic-clonic, myoclonic, spasms, with or without a trigger factor
- Sometimes seizures are related to fever, sometimes they last longer, above all in the first years of life status epilepticus may recur. In most cases the seizures disappear within the first 3-5 years of life; however, severe/medium/light psychomotor retardation can remain
- Comorbidities can be present such as language impairment, motor disturbances, behavioral disorders, orthopedic issues, visual problems, digestive difficulties, difficulty swallowing and autism.

Identify patient needs
- Parents need an adequate explanation of the diagnosis and relative prognosis with psychological support
- Parents need to be offered genetic testing
- Parents should understand that development is different from child to child
- Parents have to be sure of the diagnosis ("benign" form of KCNQ2-related epilepsies versus encephalopathy)
- Parents need to have indications of how to face up to/treat epileptic seizures and what other non-pharmacological therapies their child might need
- Parents should be informed if in their countries there are clinical studies on KCNG2 and if their child can participate.
- They must know how to keep their child safe (detect seizures at night, fever management...).
- Parents need to know what social assistance is available from the government.

Ideal results/ Support
- Genetic consultancy, explanation of causes and the possibility of reappearance.
- Professional support is given to face up to the diagnosis and the family is directed to the parent's support group and/or the association.
- Parents receive clear instructions, emergency protocol, explanation of risks and how to minimize them.
- Parents receive clear information about possible clinical studies in which their child can participate with in-depth information on risk and benefits.
- It is important for the family to know how important education and rehabilitation are for the development of the child and should be closely monitored
- The family is given a document summarizing the social benefits available and offered for the type of disease according to residency.

3. TREATMENT

Timeline: lifelong

Clinical signs / Symptoms
- Epileptic encephalopathy does not respond to medication, particularly during the first years of life. In children, seizures resolve at around 3-5 years of age, in other cases seizures persist. Treatments should aim at controlling seizure activity, mainly during infancy, and reducing side effects.
- Considerable attention should be paid to triggering factors and seizures prevention.

Identify patient needs
- Parents need counselling and professionals' help.
- Parents need information on prescribed medications, side effects, on side-effect monitoring in the long term
- Parents also need advice on how to handle triggering factors, on the condition, on the multiple issues of severe motor and cognitive impairment.
- Parents need medical help /advice on non-epileptic symptoms.
- Advice on pre-school/school/aid.
- Access to clinical trials for new treatment opportunities.

Ideal results/ Support
- A regular consultancy with health care professionals is offered.
- Up-to-date information is available for parents any time.
- Parents are informed on medication side effects and on follow-up blood test timing.
- Non-epileptic symptoms are effectively treated.
- Parents are offered support to find a school / daily assistance and care.
- Healthcare centers involve patients in research activity.
- Over the years physiatrists help families to choose devices, whose timely delivery is guaranteed by involved orthopedic units.

4. FOLLOW UP

Timeline: 2-16 years

Clinical signs/Symptoms
- Other problems like intellectual and motor disability, behavioral, orthopedic and intestinal issues may occur

Identify patient needs
- Parents need advice and evidence-based information on additional symptoms
- Parents need emotional support
- Evidence-based therapies (psychomotricity, speech therapy, postural re-education, behavioral therapy)

Ideal results/ Support
- Monitoring above mentioned issues and if possible, offering any treatment;
- Developing standards for the quality of adults' life.
- Availability of home and/or institutional care at the highest level.
- Defining a rehabilitation program (psychomotricity, speech therapy, postural re-education, behavioral therapy)

5. TRANSITION

Timeline: 16 years and up

Clinical signs / Symptoms
- Transition to adulthood
- Usually, seizures do not occur any longer. However problems relating to cognitive and motor development increase.
- Generally, patients with severe cognitive outcome show autistic behavior or are diagnosed with autism.
- Comorbidity features increase.
- In several healthcare centers the lack of cooperation between pediatricians and services oriented to adults may result in poor support for patients and their families.

Identify patient needs
- Parents need counselling and support in the transition to adulthood
- Treating adult patients, considering the severe motor impairment affecting young patients
- Monitoring development, new treatment opportunities, behavior and neuropsychological situation.

Ideal results / Support
- A transition process from pediatricians to GPs should be introduced
- Setting up of a rehabilitation plan for maintenance
- Occupational therapy / day-care centers / residential centers
- Dealing with the increase of different problems such as motor disability, swallowing issues, behavior, social and cognitive impairment.
- Community-based group homes for young adults, in view of a long-term adulthood program "during us" and perspective "after us" stages

European Reference Network

Co-funded by the European Union

Fra gendiagnostik til personlig medicin

Hvad er personlig medicin?

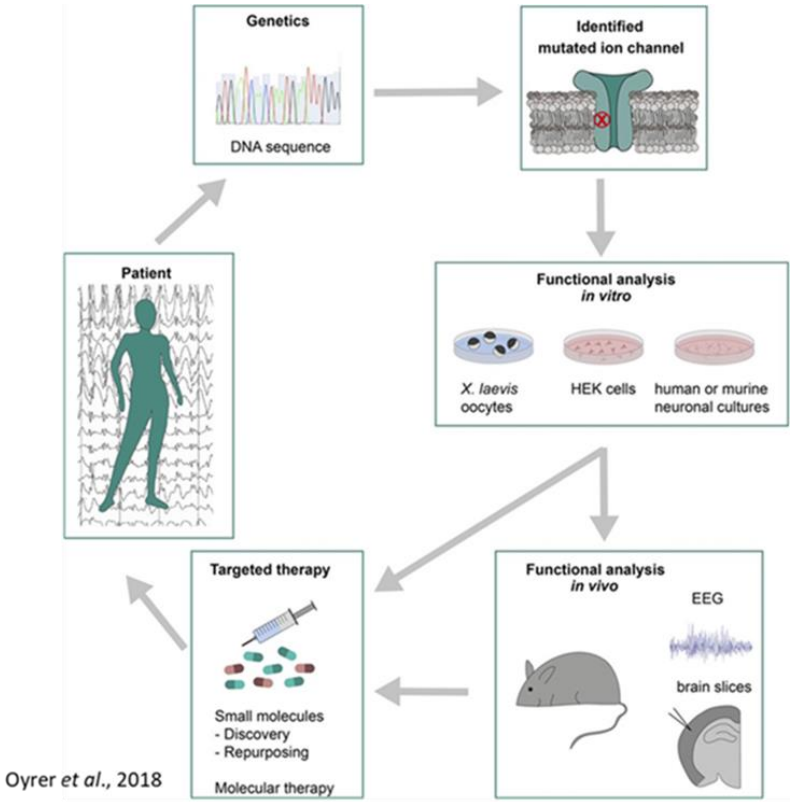
Diagnostik, forebyggelse og behandling, der i højere grad kan tilpasses den enkelte patient, omtales på forskellige måder. Det kaldes bl.a. "personlig medicin", "præcisionsmedicin", "skræddersyet medicin" og "målrettet behandling". I den nationale strategi bruges betegnelsen personlig medicin.

Personlig medicin dækker over en udvikling i sundhedsvæsenet, hvor diagnostik, forebyggelse og behandling i højere grad tilpasses den enkelte patients individuelle biologi og fysiologi samt personlige præferencer. Det kan være, at en analyse af generne kan hjælpe til at forstå, hvorfor patienten er blevet syg og dermed, hvordan patienten bedst kan behandles.

Det overordnede formål er at kunne diagnosticere og klassificere sygdomme bedre, så behandlingen kan tilpasses den enkelte patient. Det kan hjælpe til at øge effektiviteten af behandlingen og mindske bivirkninger eller at forebygge sygdom.

I denne strategi er der fokus på personlig medicin gennem anvendelsen af især genetisk information for at få indsigt i sundhed og sygdom. Det kan bruges til forebyggelse, diagnostik og behandling af sygdom, der tager højde for patientens eller sygdommens særlige biologiske forhold.

Omfattende genetisk analyse, herunder bl.a. helgenomsekventering, samkøring af data og anvendelse af materiale fra biobanker er en del af realiseringen af strategien. Anden molekylærbiologisk viden og kortlægning, som fx analysen af vores proteiner, og andre nye teknologier er dog også hastigt på vej frem og skal inddrages i strategien på sigt. Det er fx inden for billeddiagnostik, borgerskabte data og patient rapporterede oplysninger.



Oyrer *et al.*, 2018

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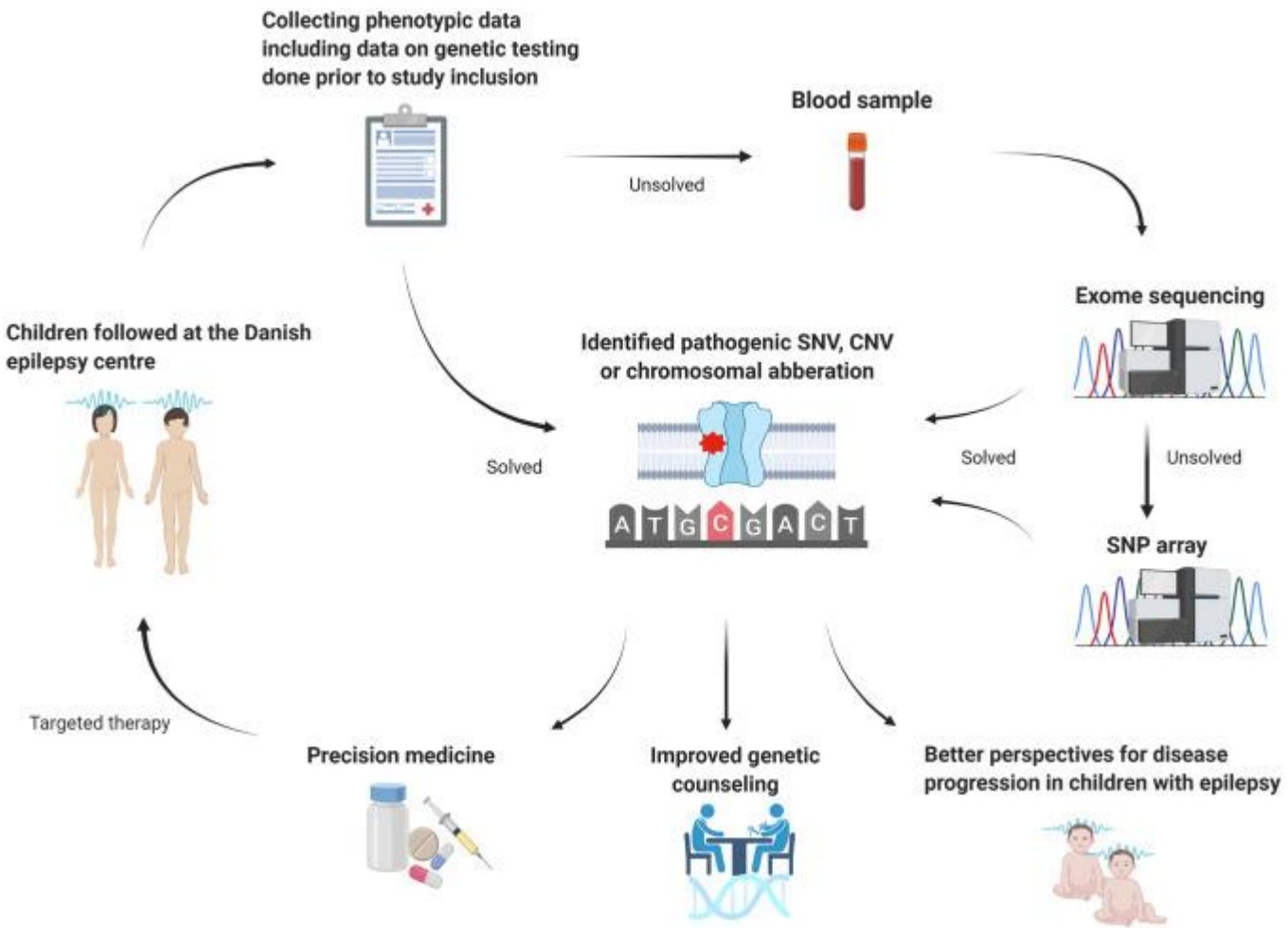
FILADELFIA

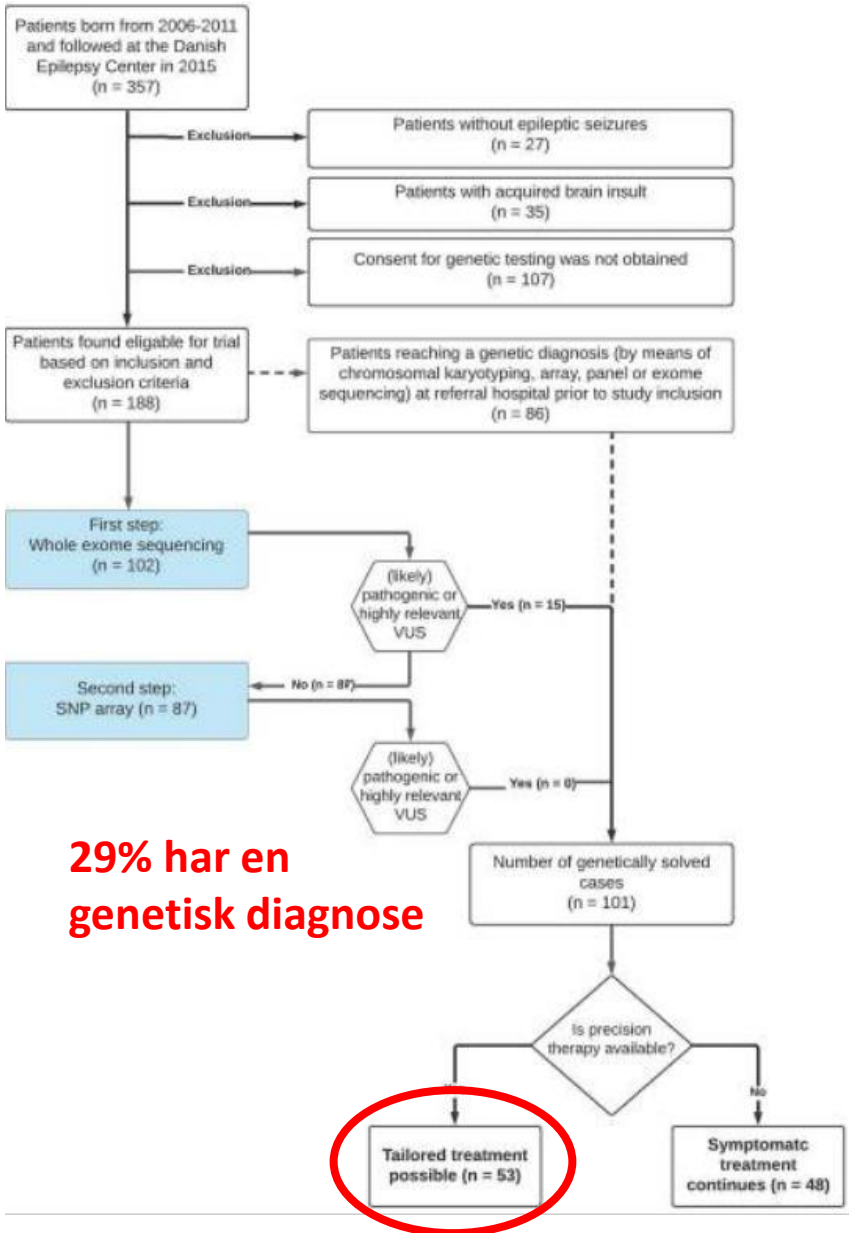
Neurotherapeutics (2022) 19:1353–1367
https://doi.org/10.1007/s13311-022-01264-1

ORIGINAL ARTICLE

Impact of Genetic Testing on Therapeutic Decision-Making in Childhood-Onset Epilepsies—a Study in a Tertiary Epilepsy Center

Allan Bayat[1,2] · Christina D. Fenger[1,3] · Tanya R. Techlo[4] · Anne F. Højte[1] · Ida Nørgaard[3] · Thomas F. Hansen[4,5] · Guido Rubboli[1,6] · Rikke S. Møller[1,2] · Danish Cytogenetic Central Registry study group

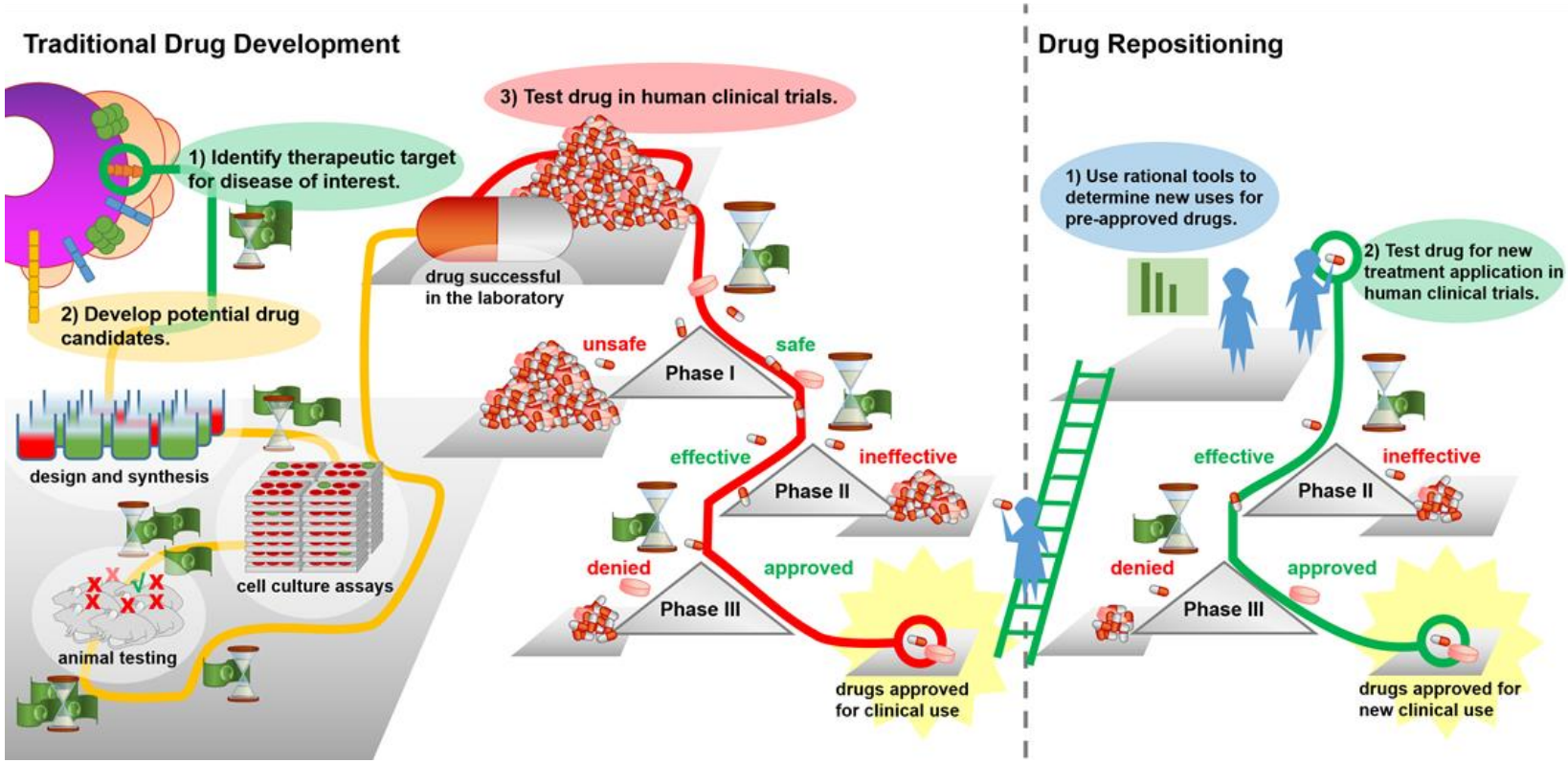




29% har en genetisk diagnose

Genanvendelse af allerede eksisterende lægemidler

En proces, hvor man identificerer nye terapeutiske anvendelses-former for gamle/ eksisterende/ tilgængelige lægemidler



https://i0.wp.com/sitn.hms.harvard.edu/wp-content/uploads/2016/05/05-02-2016_Figure1_v1.png

GENFORSØG I CELLE FRA HAMSTER VISTE VEJ TIL GAMMEL LYKKEPILLE, DER KUNNE HJÆLPE MOD FREJS EPILEPSI

> En genetisk diagnose giver mulighed for at finde skræddersyet medicin, der kan hjælpe mod epilepsien, men som måske er udviklet til helt andre sygdomme. Forældre skal indsamle 400.000 kr. til jagten på den mest optimale medicin til deres søn.

Take home messages

- Genetiske faktorer spiller en vigtig rolle ved epilepsi
- Ikke alle er kandidater til genetisk udredning
- En genetisk diagnose kan have mange fordele, men giver ikke altid svar på alt
- Første skridt på vejen mod præcisions-behandling er præcisions-diagnostik
- Skræddersyede behandlingsformer vinder mere og mere frem, men er stadig kun tilgængelige for en mindre gruppe af personer med epilepsi

Hvem kan I rådføre jer med?

- Epilepsiforeningen
- Egen læge/børnelæge/neurolog
- Klinisk Genetiske Afdelinger: Alle monogene sygdomme (kræver henvisning)
- Afdeling for epilepsigenetik og personlig medicin, Filadelfia (genetics@filadelfia.dk) (kræver evt henvisning)
- Center for Sjældne sygdomme: Syndrom mistanke (kræver henvisning)

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