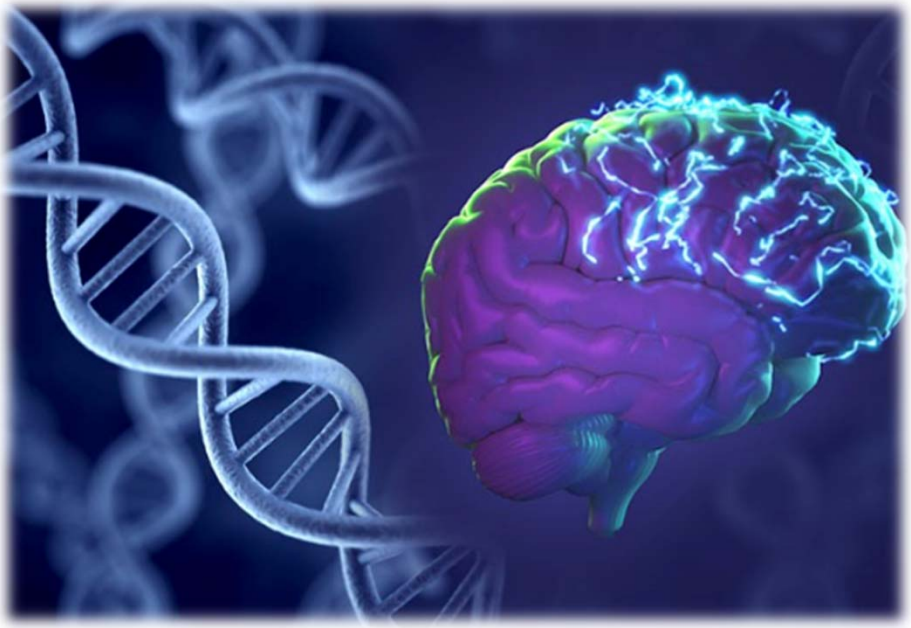
Epilepsy Update & Review Course 2020

Selecting the Correct Genetic Test and Interpretation in Epilepsy



Cleveland Clinic

Mo, Sep 21st, 2020

Dennis Lal, PhD – Assistant Professor for Molecular Medicine

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Genomic Medicine Institute, Lerner Research Institute ***Cleveland Clinic, Cleveland, Ohio, USA***
Stanley Center for Psychiatric Research, ***Broad Institute of Harvard and M.I.T., Cambridge, USA***
Cologne Center for Genomics, ***University of Cologne, Cologne, Germany***

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@LalDennis

Why is genetic testing useful in caring for epilepsy patients?

- Understanding the genetic basis of the condition might help give information about the **progress** of the condition, possible **preventive actions** or **treatment**.

- Patients with a genetic condition may just find it helpful to know why their signs and symptoms occur.
  - Many Gene-Disorder Family Organizations have been formed **raising funds for research** and **provide support** for new patients and families.

Examples of precision medicine in epilepsy

Table1: Precision medicine examples of frequently mutated epilepsy genes. *AED = Anti-Epileptic Drug, GOF = Gain-of-function variant, LOF = Loss-of-function variant, data selected from recent reviews*[9–11].

Gene	AEDs/treatments recommended	AED to avoid	Other management Implications	Rate of precision medicine responders
SLC2A1	Ketogenic Diet	-	-	Most respond
ALDH7A1 and PNPO	Pyridoxine	-	Lysine-restricted diet	A minority responds
SCN1A	Stiripentol, Valproate, Clobazam, Ketogenic Diet Cannabidiol, Fenfluramine	Phenytoin/Carbamazepine /Lamotrigine/Oxcarbazepine		Minority responds to the current treatment regime, but clinical trials with Fenfluramine look promising
SCN2A	*SCN2A*-GOF: Carbamazepine, phenytoin, Oxcarbazepine	*SCN2A*-LOF: Carbamazepine, phenytoin, Oxcarbazepine	Consider high-dose IV phenytoin for status epilepticus	Variable response rates for *SCN2A*-GOF
SCN8A	Carbamazepine, phenytoin, Oxcarbazepine	-	-	Minority respond. It depends if mutations lead to gain- or loss-of-function
KCNQ2	Carbamazepine, phenytoin, Retigabine	-	-	Minority responds. It depends if mutations lead to gain- or loss-of-function
PCDH19	Clobazam, steroids	-	-	Minority responds
PRRT2	Carbamazepine	-	-	Majority responds
KCNT1	Trial of Quinidine in early-onset seizures, Potassium bromides, Ketogenic Diet, Vigabatrin	-	-	Minority responds

Scheffer et al ., 2020 Eur J Paediatr Neurol.
Musto E et al., 2019 Eur J Paediatr Neurol.
Symonds JD, McTague A. 2020 Eur J Paediatr Neurol.

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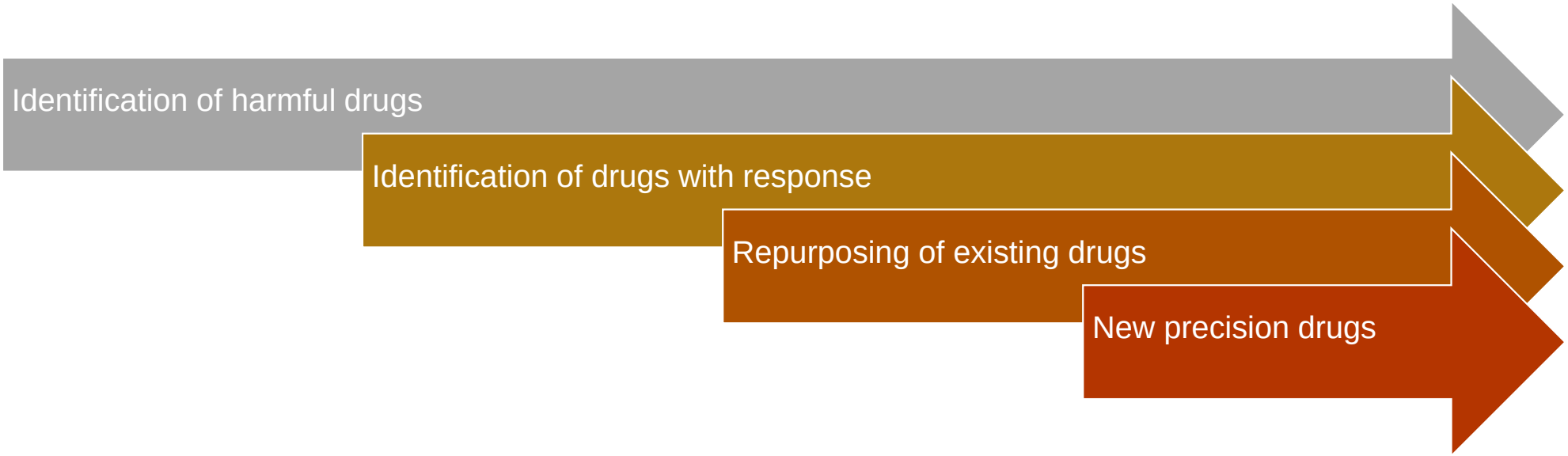
Precision medicine in epilepsy – where are we?



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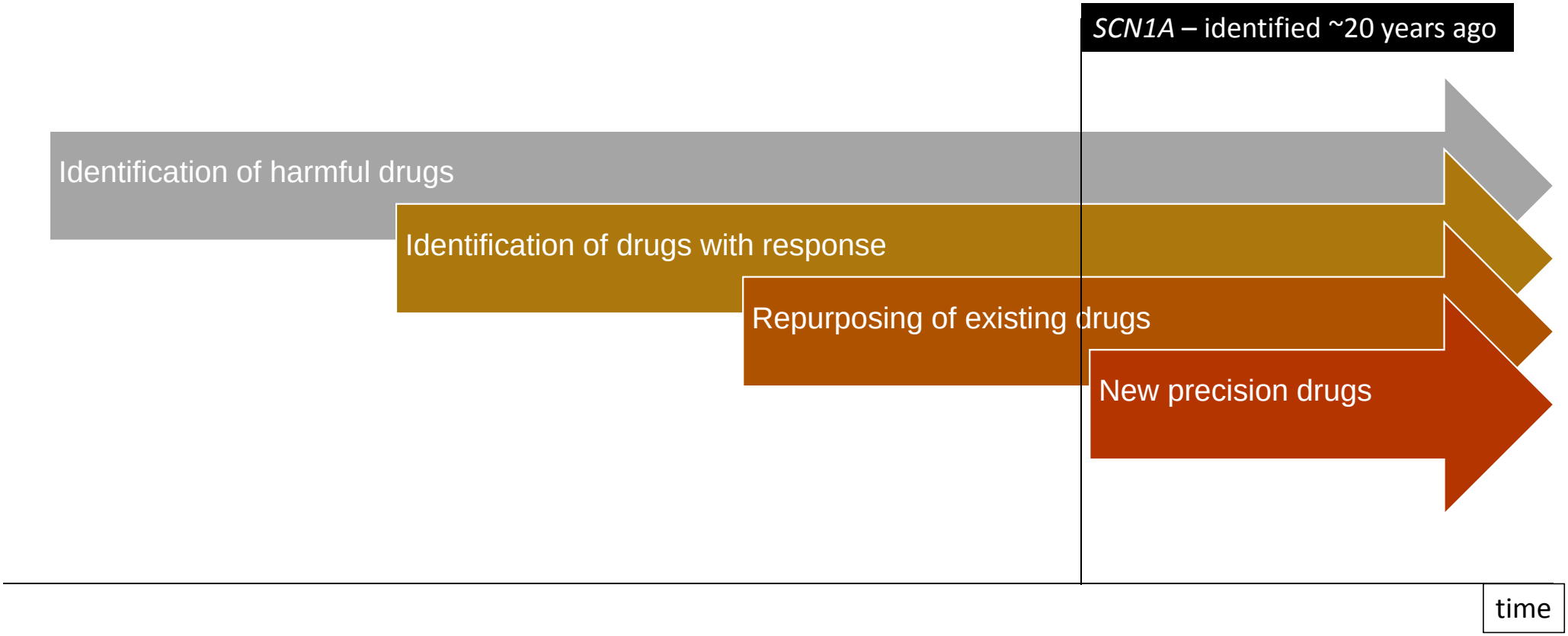

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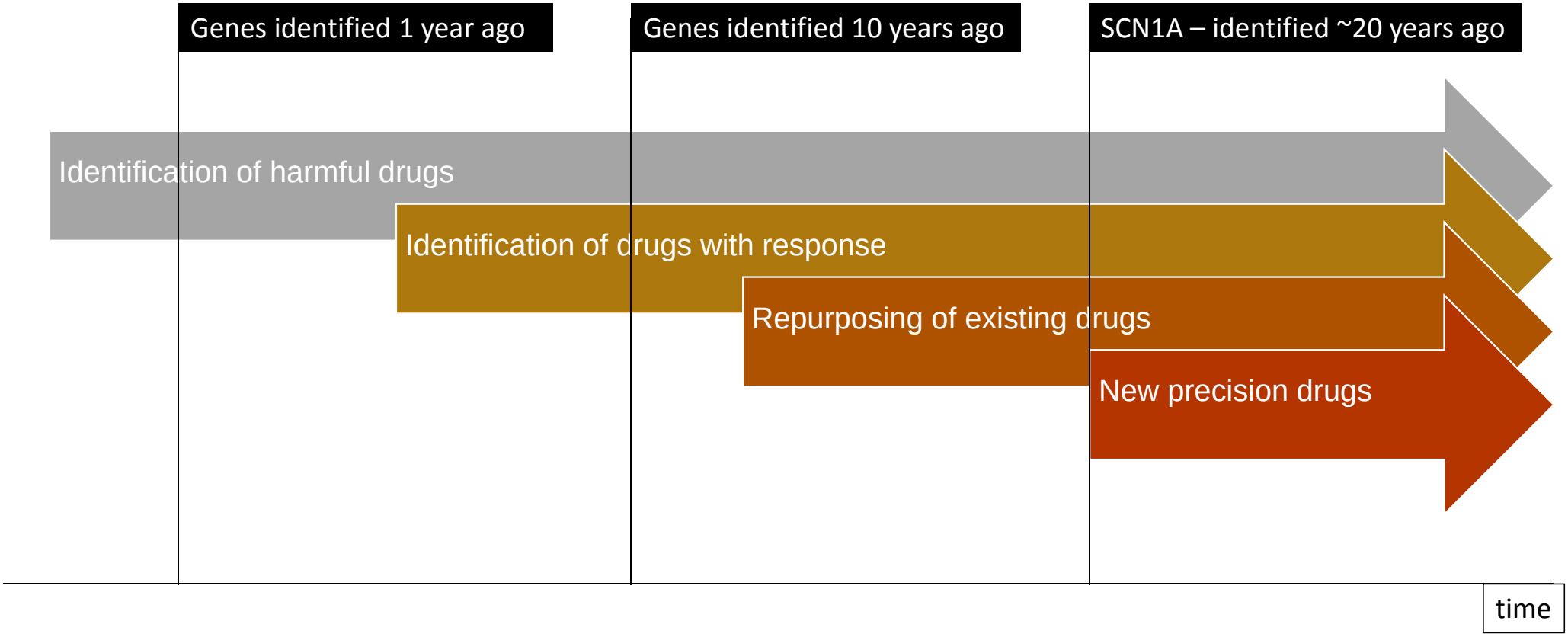
Precision medicine in epilepsy – where are we?



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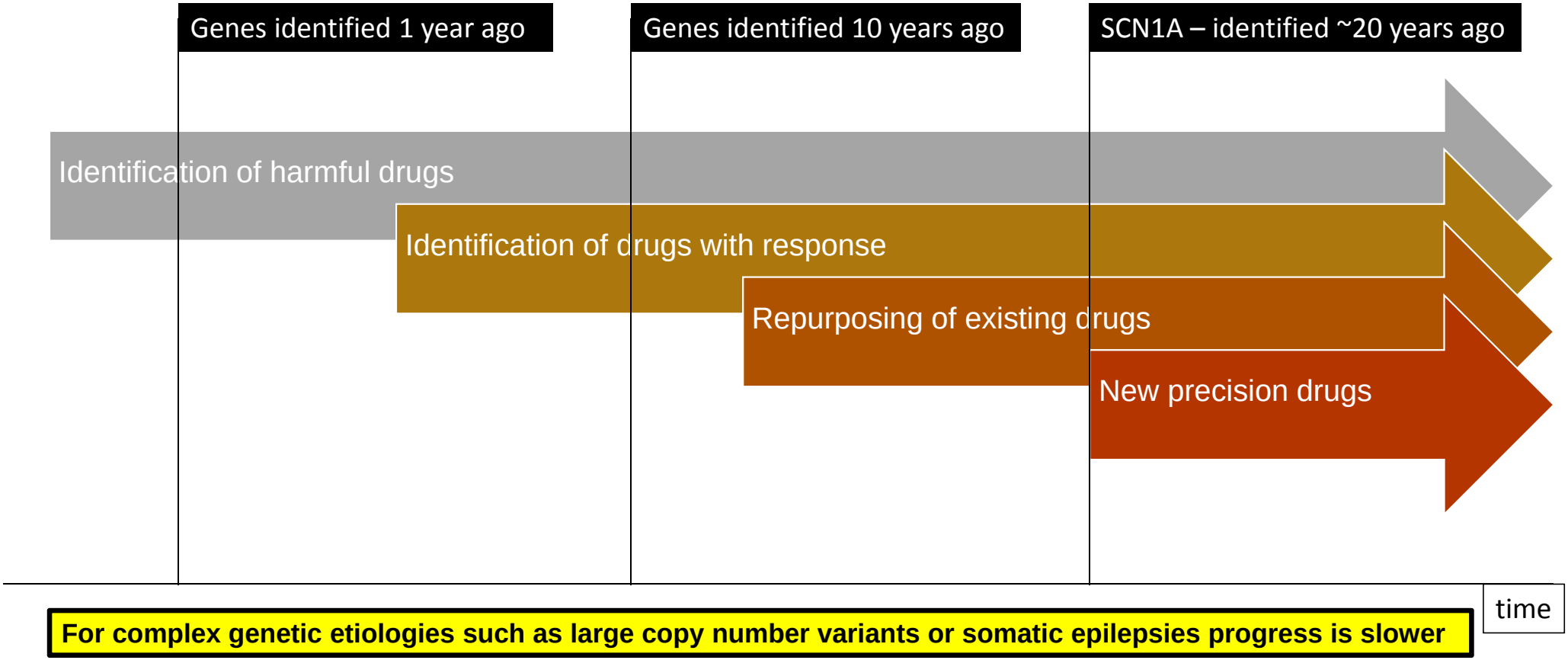
Precision medicine in epilepsy – where are we?



For complex genetic etiologies such as large copy number variants or somatic epilepsies progress is slower

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What % of epilepsy patients are “genetic”?

We don’t know.

A population based comprehensive genetic screen across all age ranges and tissue types has not been performed.

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Most epilepsy genetic cohort screening studies focus on epilepsy subtypes, ascertained through tertiary care centers & perform targeted testing of rare variants

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What % of epilepsy patients are “genetic”?

We tried to answer this question based on (incomplete) data available

Arthur Stefanski

Stefanski et al., 2020 in review

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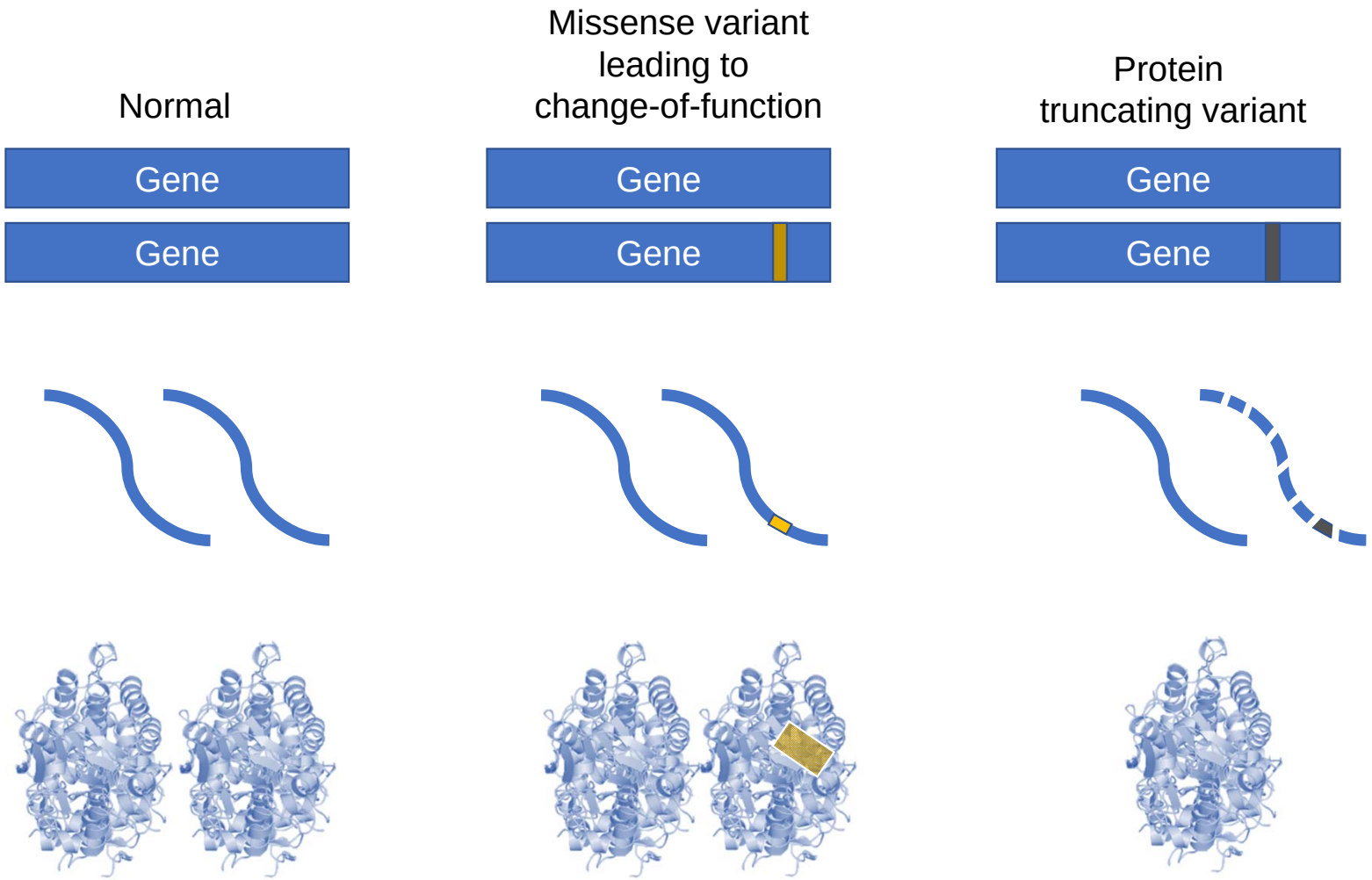
Most common clinically screened types of pathogenic genetic variants



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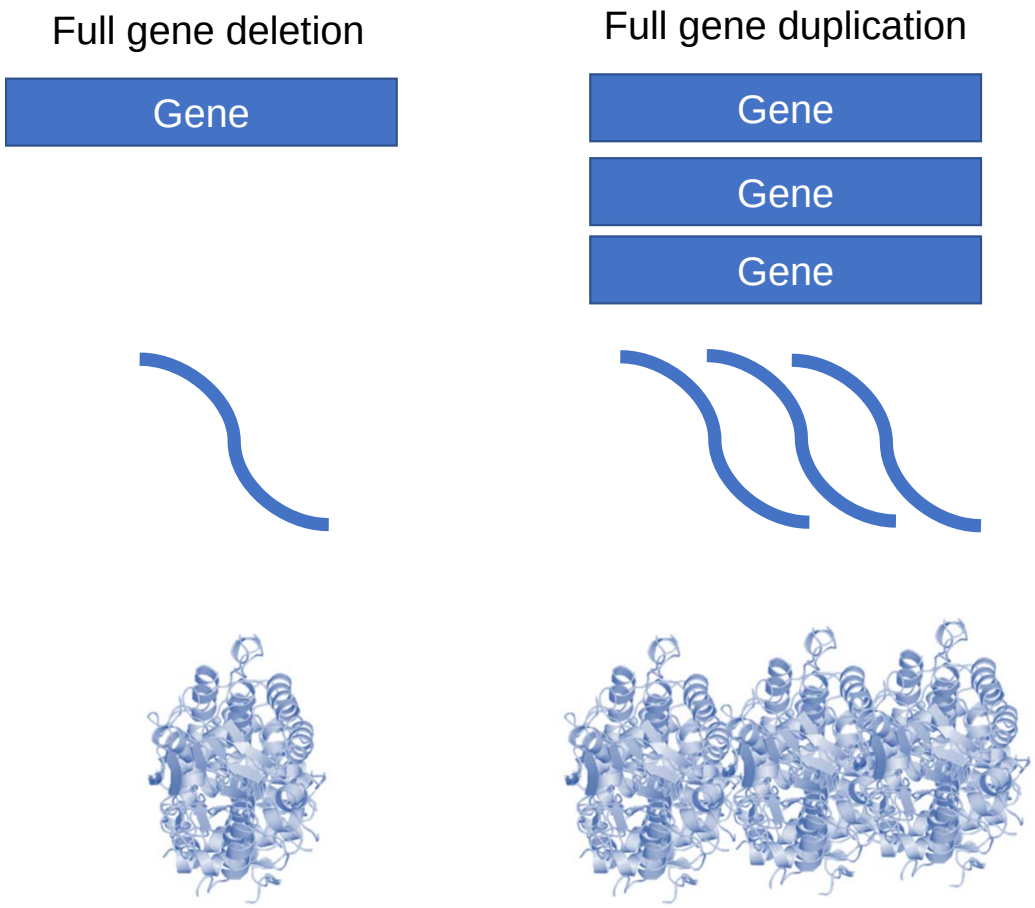

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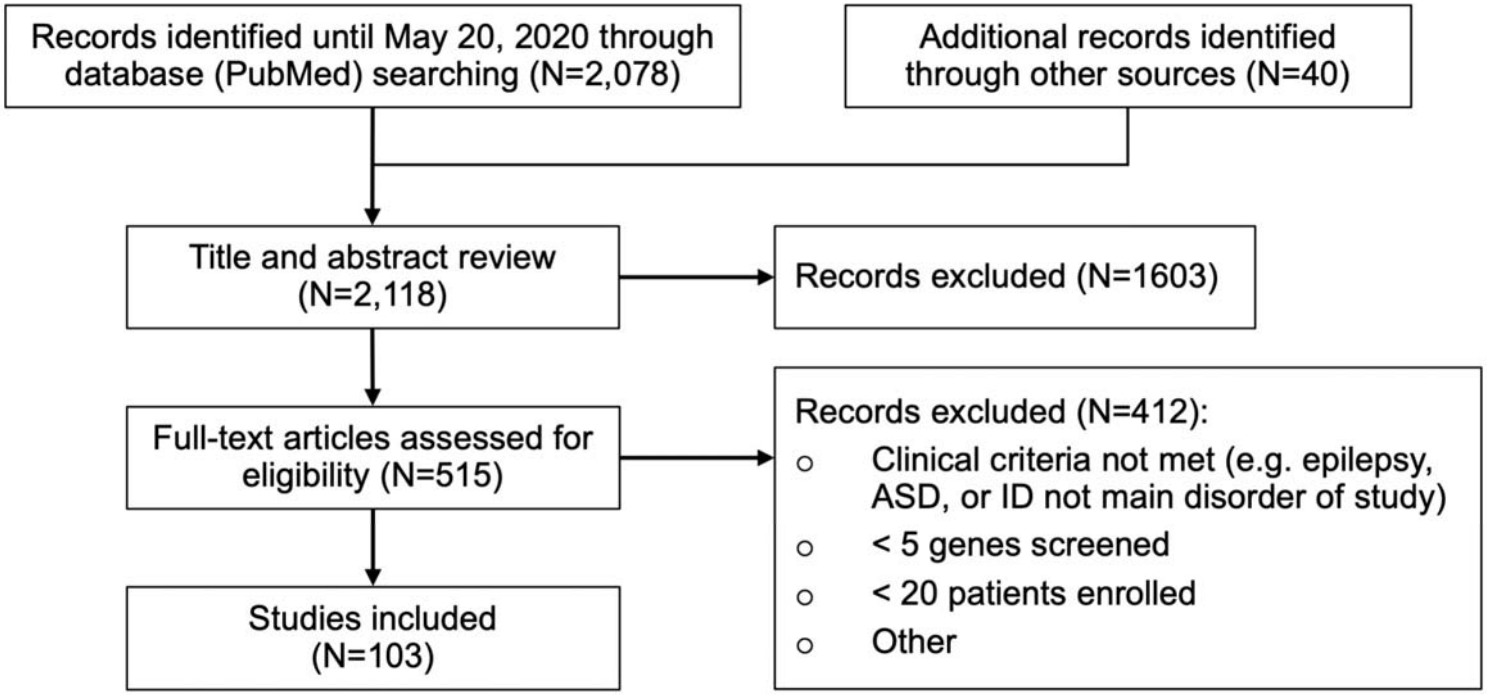
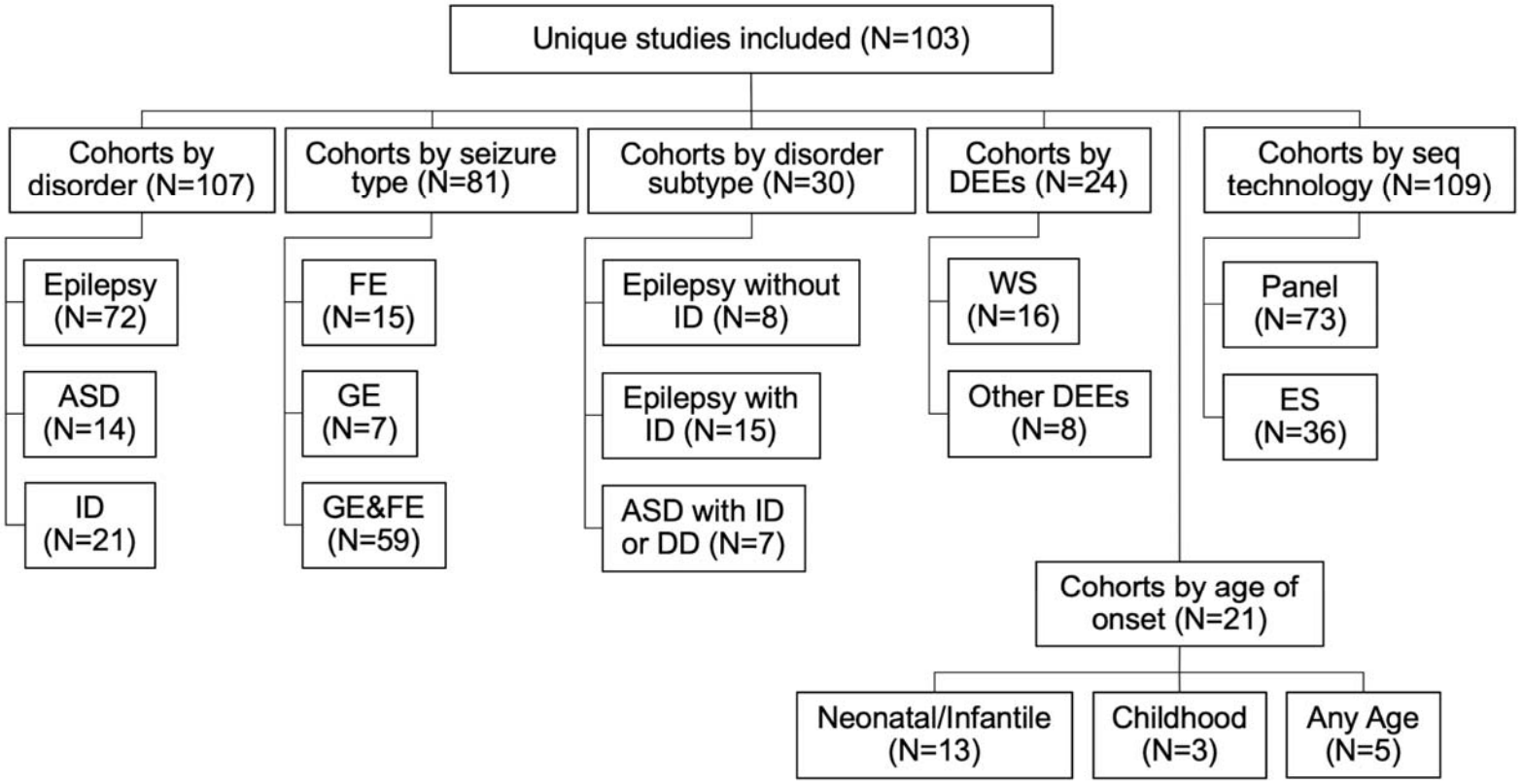
We identified 103 studies, including 72 epilepsy specific ones, to estimate the % of genetic test positive people with a neurodevelopmental disorder



The 103 studies were categorized for additional downstream analyses



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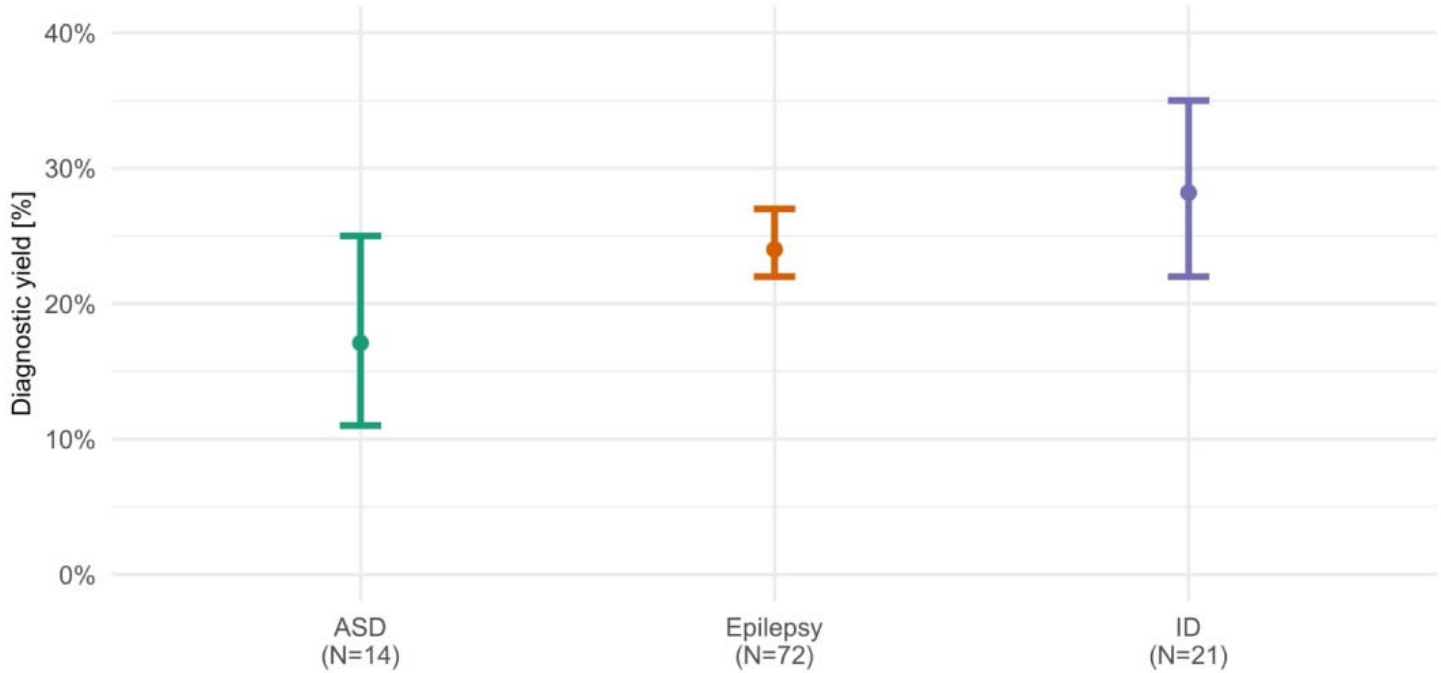
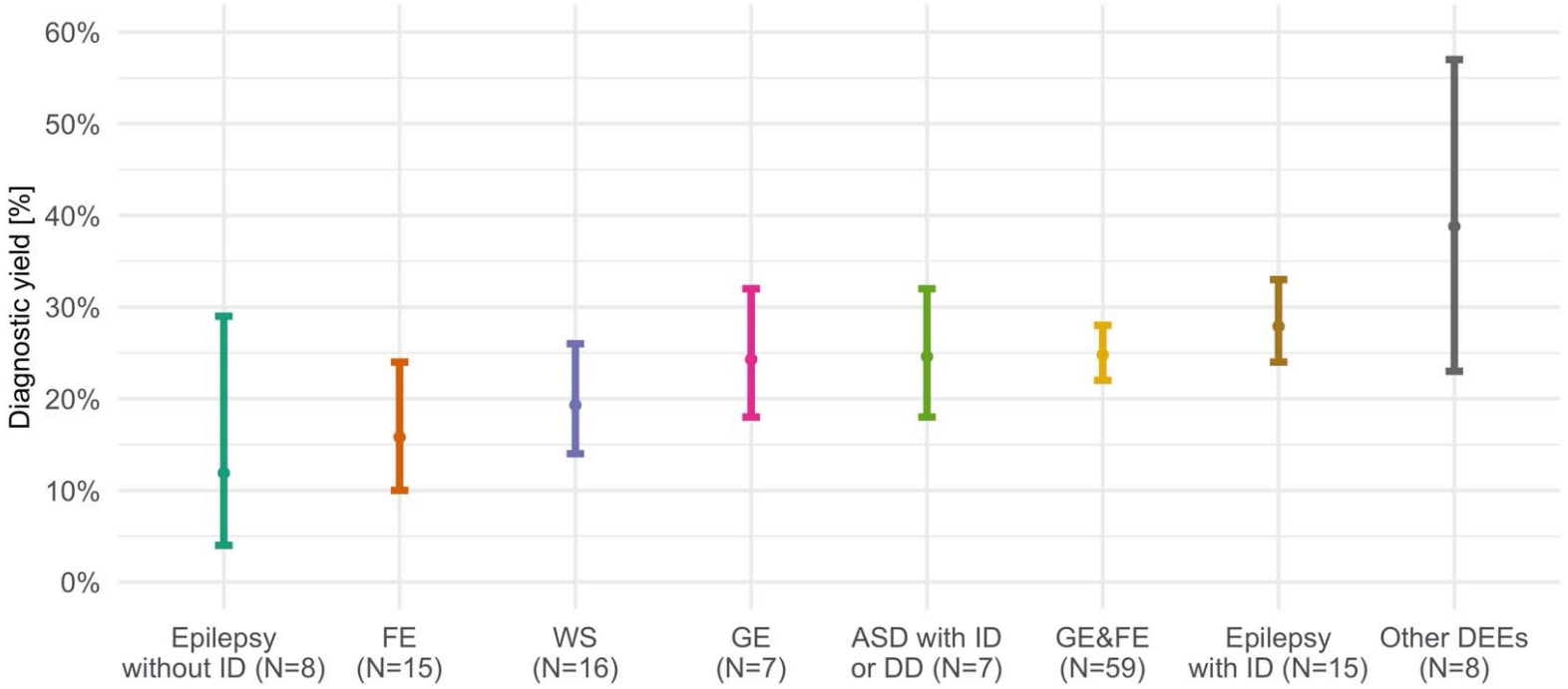
In the disorder analysis about 1 in 3-6 people with a neurodevelopmental disorder are genetic test positive



Abbreviations: ASD = autism spectrum disorder, ID = intellectual disability.

Epilepsy patients with cognitive problems have greater genetic burden



Abbreviations: GE&FE = combined generalized and focal epilepsy, FE = focal epilepsy, GE = generalized epilepsy, WS = West syndrome, ASD with ID or DD = autism spectrum disorder with intellectual disability or developmental delay.

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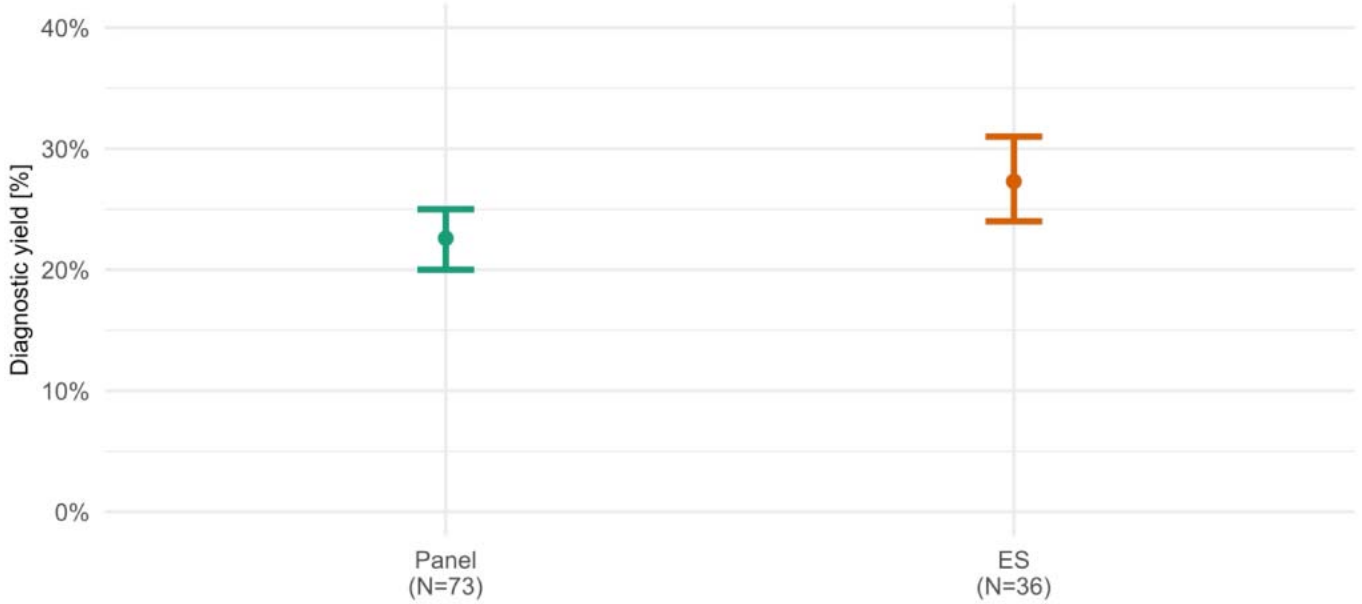
Diagnostic yield is higher in Whole Exome Sequencing vs. gene panel sequencing studies



The diagnostic yield across Panel and ES.

Abbreviations: Panel = targeted gene panel sequencing, ES = exome sequencing.

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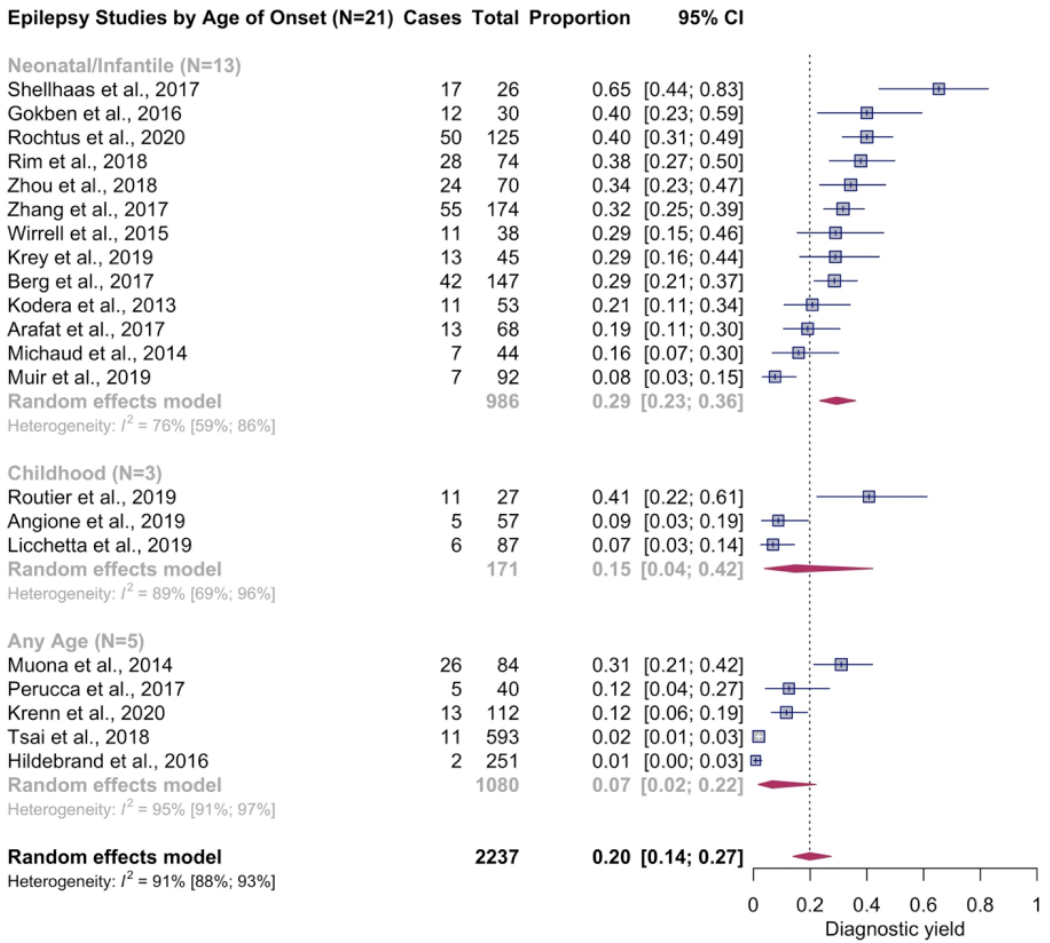
Diagnostic yield in early onset epilepsies is greater compared to later onset epilepsies



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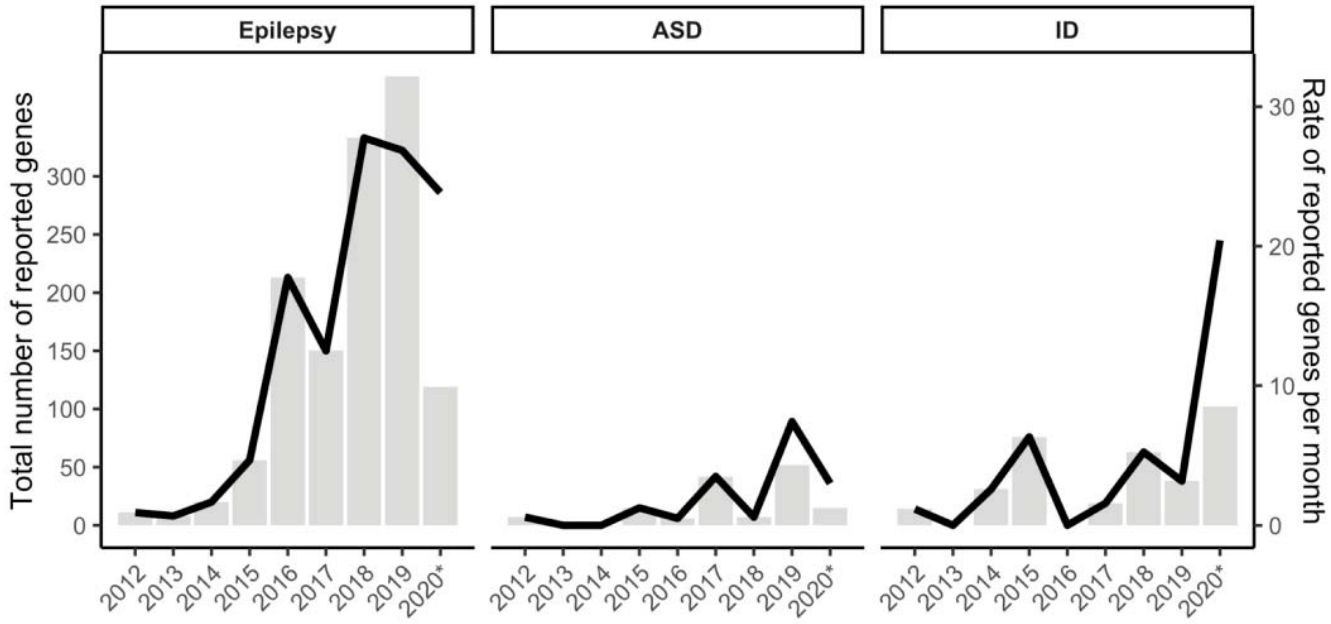
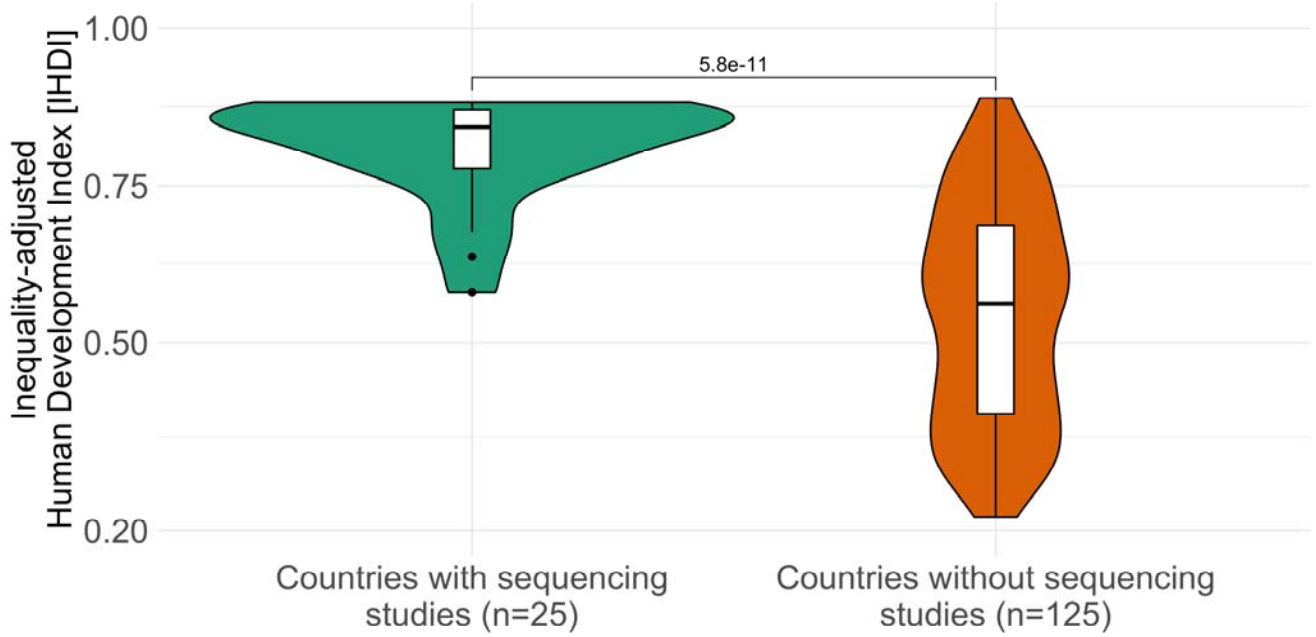
The number of genes with pathogenic variant is still increasing



The bars represent the number of genes with pathogenic variants. The line represents the rate of genes per month and year. The number of identified genes increased rapidly in recent years for epilepsy. For ASD and ID the number of reported genes with pathogenic v*ariants is low. Abbreviations: ASD = autism spectrum disorder, ID = intellectual disability,* * = Data were collected until May 20, 2020.

Likely health disparities: No access to genetic testing?



Countries with sequencing studies have a significantly higher mean Inequality-adjusted Human Development Index (IHDI), compared to countries without sequencing studies(P = 5.8x10^{-11})

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Summary of our meta-analysis

- 1 in 2-12 people with epilepsy with receive a diagnosis through currently available genetic tests
- Earlier epilepsy onset and cognitive challenges increase the chance of a positive genetic test
- More comprehensive genetic tests have a greater diagnostic yield
- The number of epilepsy-associated genes is increasing
- Not everyone has access to genetic testing

Arthur Stefanski

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What did the studies miss?
-> Most studies analyzed only known epilepsy genes

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There a several classes of epilepsy associated genetic variants, which are currently not routinely screened or interpreted

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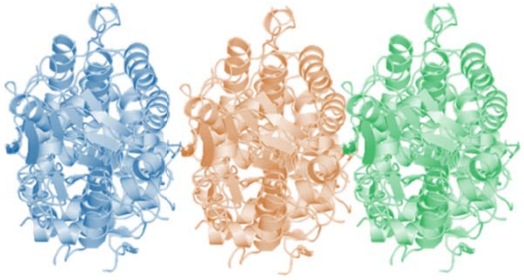
Large pathogenic copy number variants not affecting an established epilepsy gene

DNA level

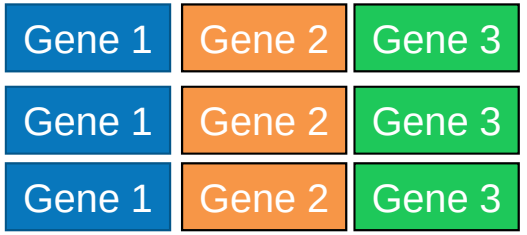
mRNA level

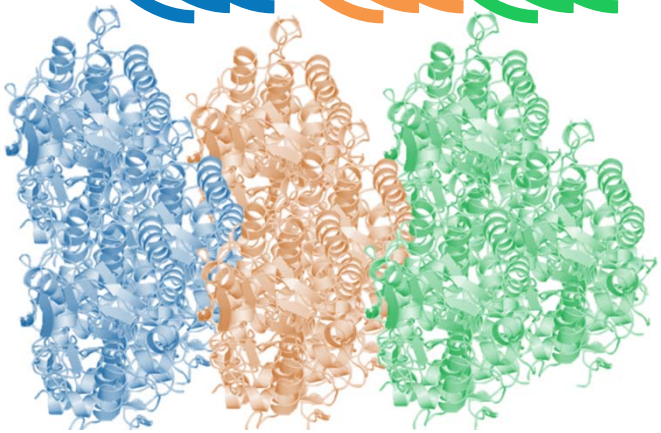
Protein level

Large multi-gene deletion

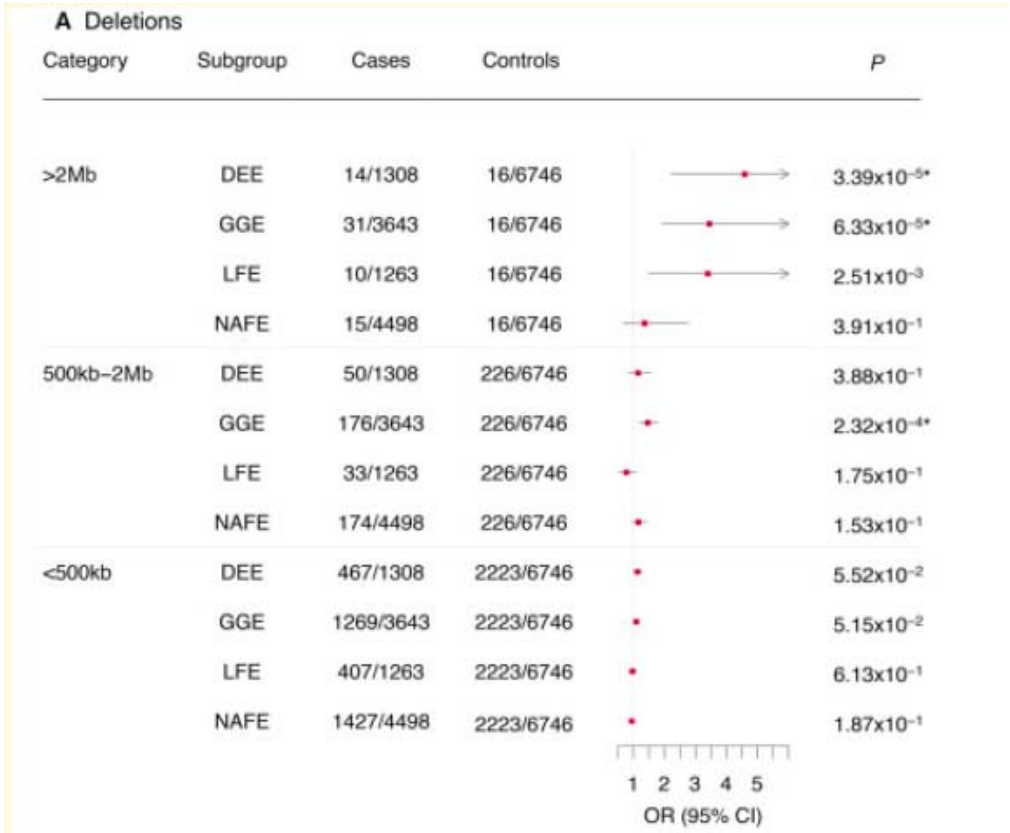


Large multi-gene duplication





Large pathogenic copy number variants not affecting an established epilepsy gene



doi:10.1093/brain/awaa171 BRAIN : Page 1 of

BRAIN
A JOURNAL OF NEUROLOGY

Epilepsy subtype-specific copy number burden observed in a genome-wide study of 17 458 subjects

Lisa-Marie Niestroj,[1] Eduardo Perez-Palma,[2] Daniel P. Howrigan,[3] Yadi Zhou,[2] Feixiong Cheng,[2,4,5] Elmo Saarentaus,[6] Peter Nürnberg,[1,7,8] Remi Stevelink,[9,10] Mark J. Daly,[3,6,11] Aarno Palotie[3,6,11] and Dennis Lal[1,2,3,12] on behalf of the Epi25 Collaborative*

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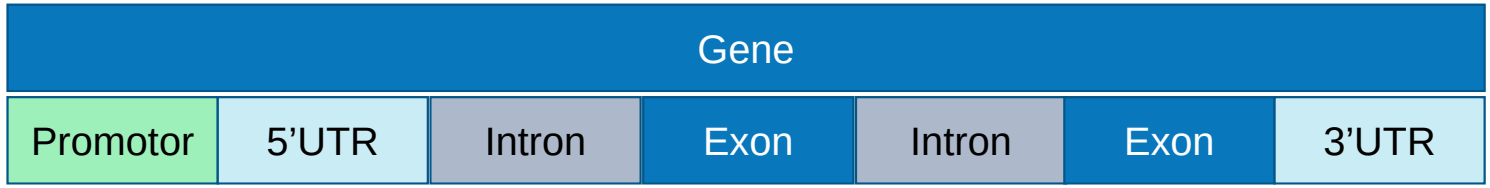
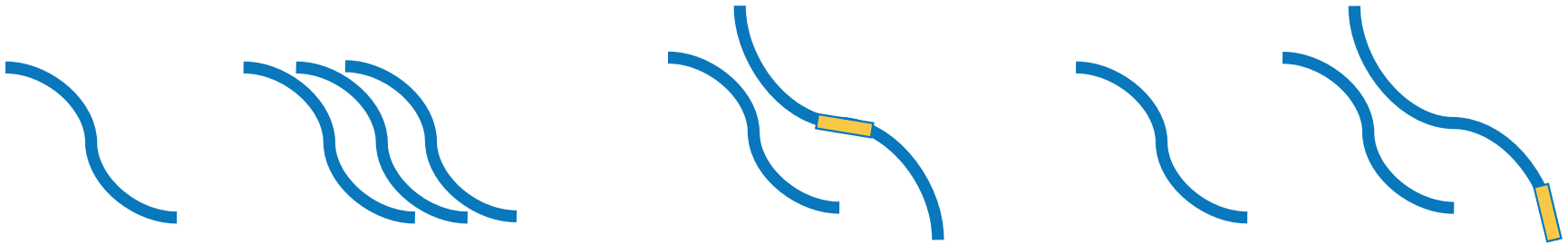
Nucleotide expansion pathogenic genetic variants

DNA level

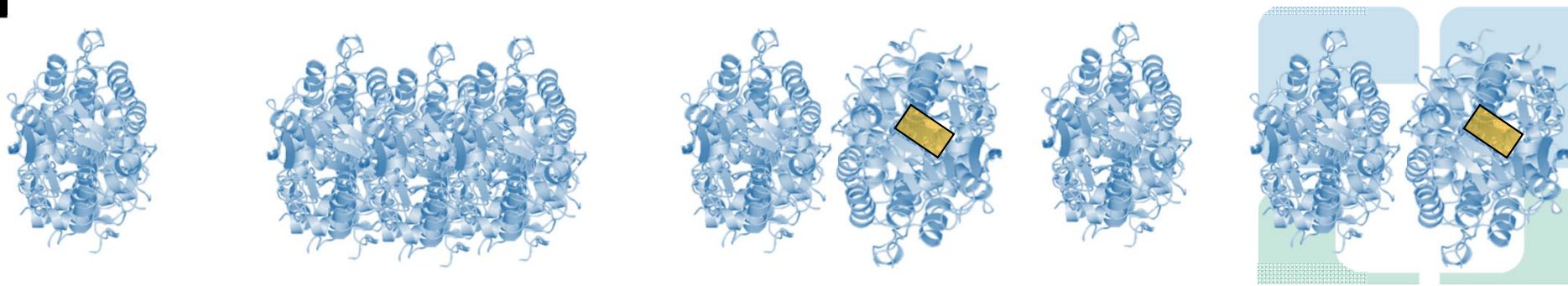
Nucleotide expansion disorders affecting different parts of a gene



mRNA level



Protein level



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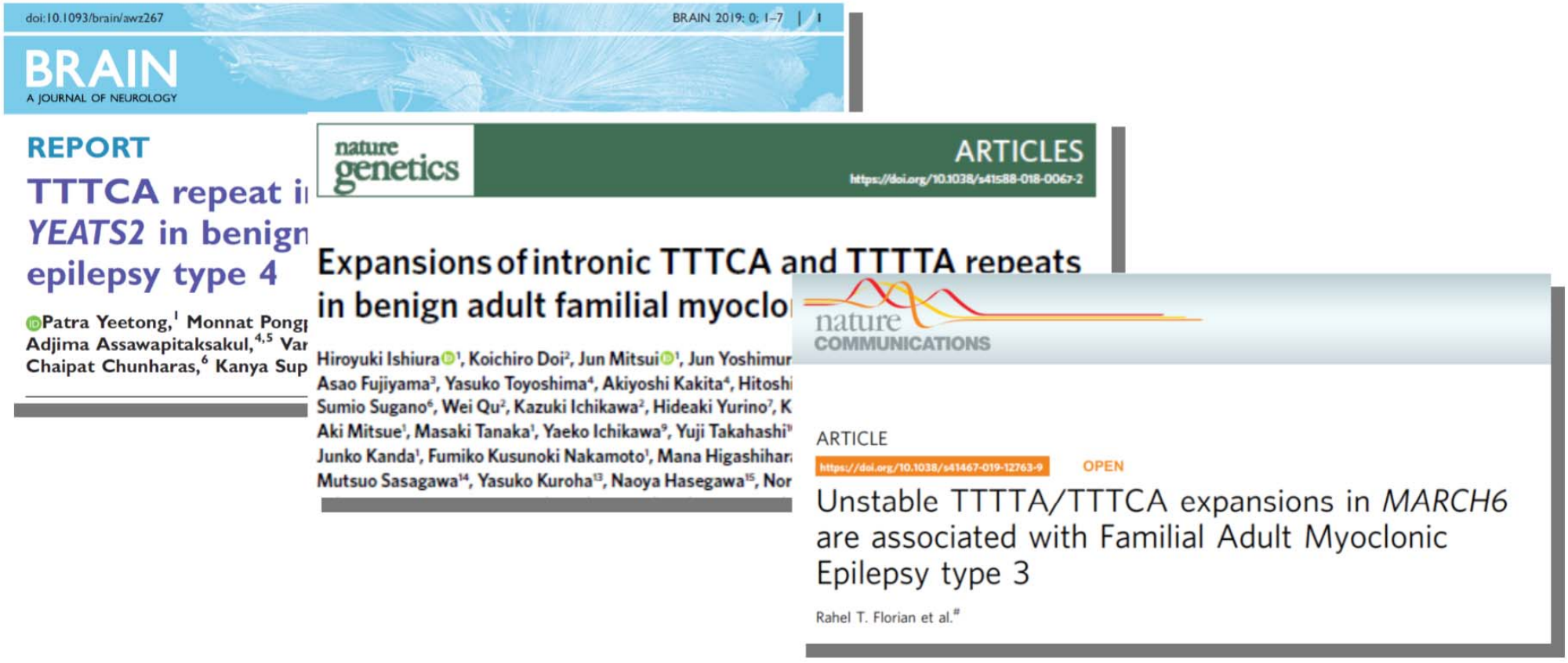
Types of nucleotide repeat pathogenic genetic variants



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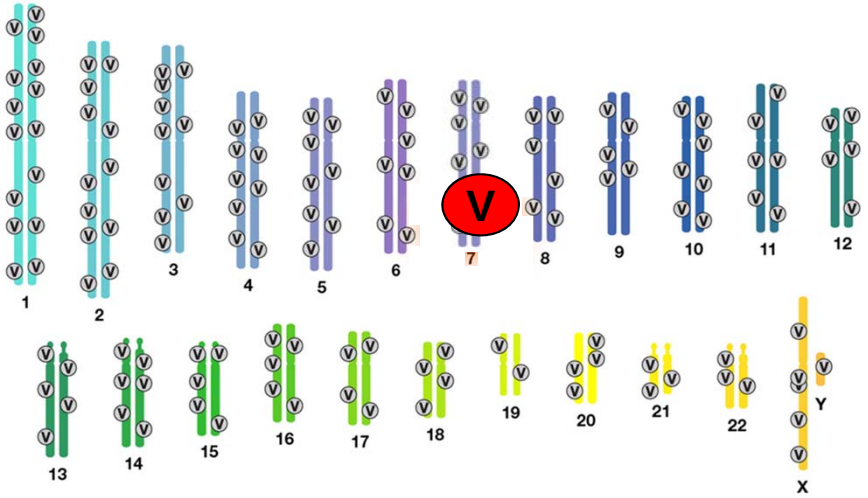
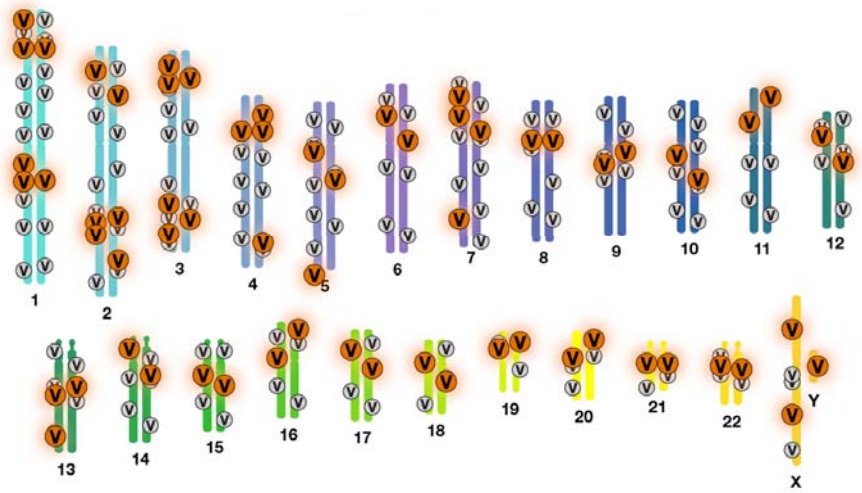
Polygenic disease ‘risk’ variants

A person with a disease causing variant on chromosome 7



A person with thousands of disease risk conferring variants across the genome



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Polygenic disease ‘risk’ variants

doi:10.1093/brain/awz292 BRAIN 2019: 142; 3473–3481

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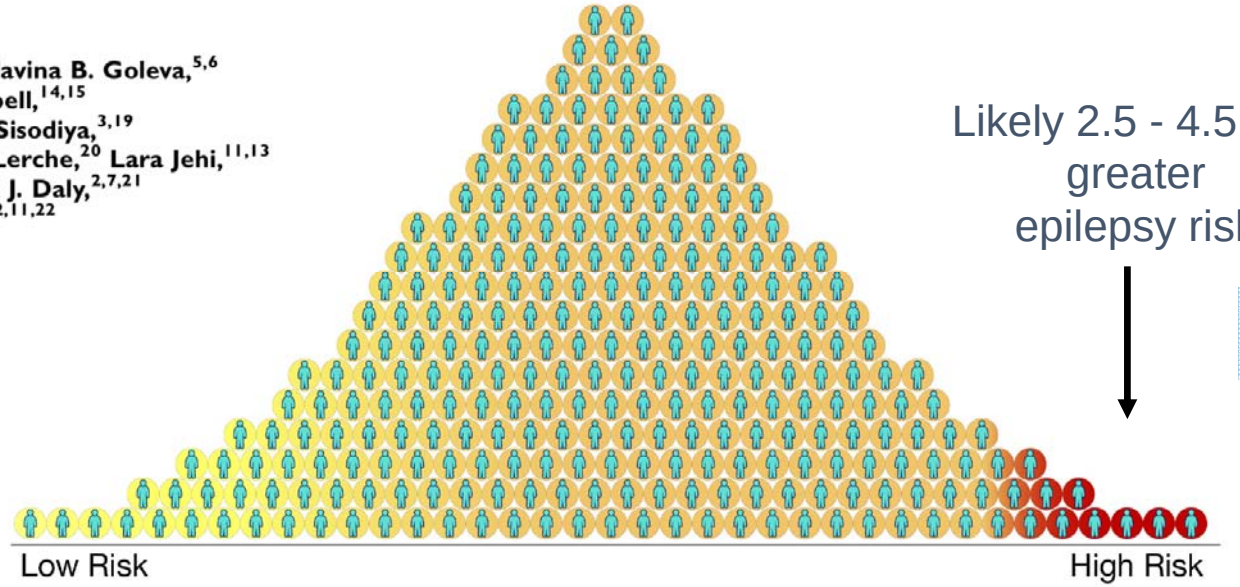
Polygenic burden in focal and generalized epilepsies

Costin Leu,[1,2,3] Remi Stevelink,[4] Alexander W. Smith,[2] Slavina B. Goleva,[5,6] Masahiro Kanai,[2,7,8,9,10] Lisa Ferguson,[11,12,13] Ciaran Campbell,[14,15] Yoichiro Kamatani,[10,16] Yukinori Okada,[10,17,18] Sanjay M. Sisodiya,[3,19] Gianpiero L. Cavalleri,[14,15] Bobby P.C. Koeleman,[4] Holger Lerche,[20] Lara Jehi,[11,13] Lea K. Davis,[5,6] Imad M. Najm,[11,13] Aarno Palotie,[2,21] Mark J. Daly,[2,7,21] Robyn M. Busch,[11,12,13] Epi25 Consortium and Dennis Lal[1,2,11,22]



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Somatic variants

- An underlying disease causing genetic variant can be identified in 1 in 2-9 patients with a lesional epilepsy (e.g., low grad tumors or cortical malformation)

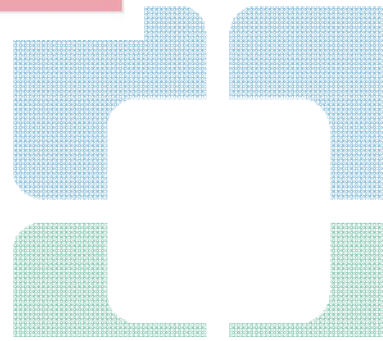
- Examples of focal cortical dysplasia brain tissue sequencing studies

Study	Total sample size	FCD I	FCD II	Carrier of somatic variants	Success rate (% yield)
Zhang et al. (2020)	17	0	17	7	41.18
Baldassari et al. (2019)	80	18	62	37	46.25
Sim et al. (2019)*	75	4	71	18	24.00
Niestroj et al. (2019)	15	0	15	2	13.33
Zhao et al. (2019)	8	0	8	1	12.50
D'Gama et al. (2017)	66	0	66	14	21.21
Lim et al. (2017)	40	0	40	5	12.50
Møller et al. (2016)	19	3	16	6	31.58
Mirzaa et al. (2016)	8	0	8	4	50.00
Nakashima et al. (2015)	24	6	18	6	25.00
Lim et al. (2015)	77	0	77	12	15.58
Jansen et al. (2015)	33	0	33	4	12.12
D'Gama et al. (2015)	53	0	53	6	11.32
Total (no duplicates)	491	31	460	122	24.85

Variant interpretation is in its infancy

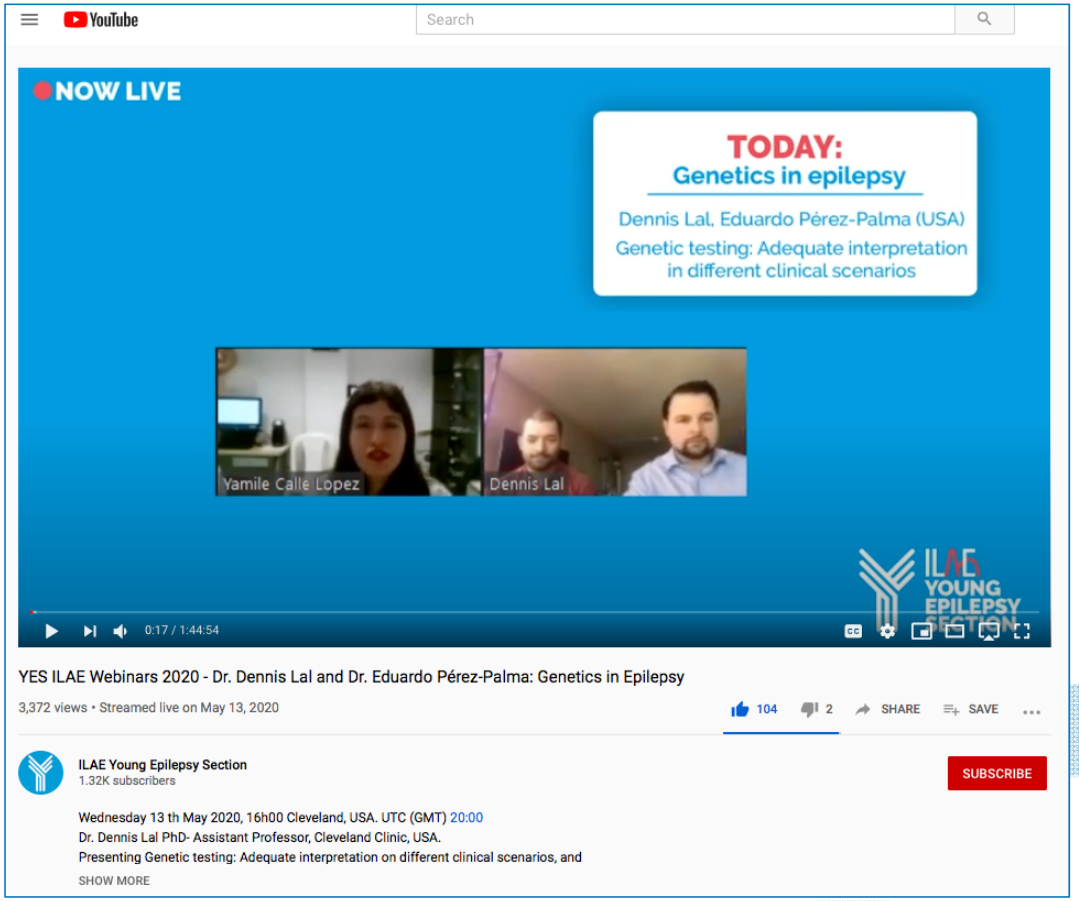
Important to acknowledge!

- Rare missense variants are not rare as an aggregate
- The chance to find in a genetic test a benign variant in a epilepsy gene that 'fits the broader phenotype' is high
- A large amount of previous pathogenic classified variants found in disease databases are becoming now reclassified as benign



Resources relevant for variant interpretation

- We have a ~2h overview presentation online in the young epilepsy ILAE youtube channel



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Summary

- 1 in 2-12 people with epilepsy with receive a diagnosis through currently available genetic tests
- Earlier epilepsy onset and cognitive challenges increase the chance of a positive genetic test
- More comprehensive genetic tests have a greater diagnostic yield
- The number of epilepsy-associated genes is increasing
- Not everyone has access to genetic testing
- **Several in ’research well-established’ different types of pathogenic or risk variants are currently not screened in the clinic. This will change in the near future. Subsequently, the role of genetics in clinical management of patients will further increase.**
- **Not all varriants identified in clinical genetic testing are pathogenic**

Acknowledgement

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