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Epilepsie im Vogelflug

Steffen Syrbe, Heidelberg

Interessenskonflikte

- Beratungshonorar:
 - Zogenix
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 - UCB
 - Orion Pharma
 - Eisai
 - Jazz Pharmaceuticals
 - PRECISIS

Welche Rolle spielen genomische Mikrodeletionen /
Mikroduplikationen bei Epilepsie und
neuropsychiatrischen Erkrankungen mit epileptischen
Anfällen?

nature communications



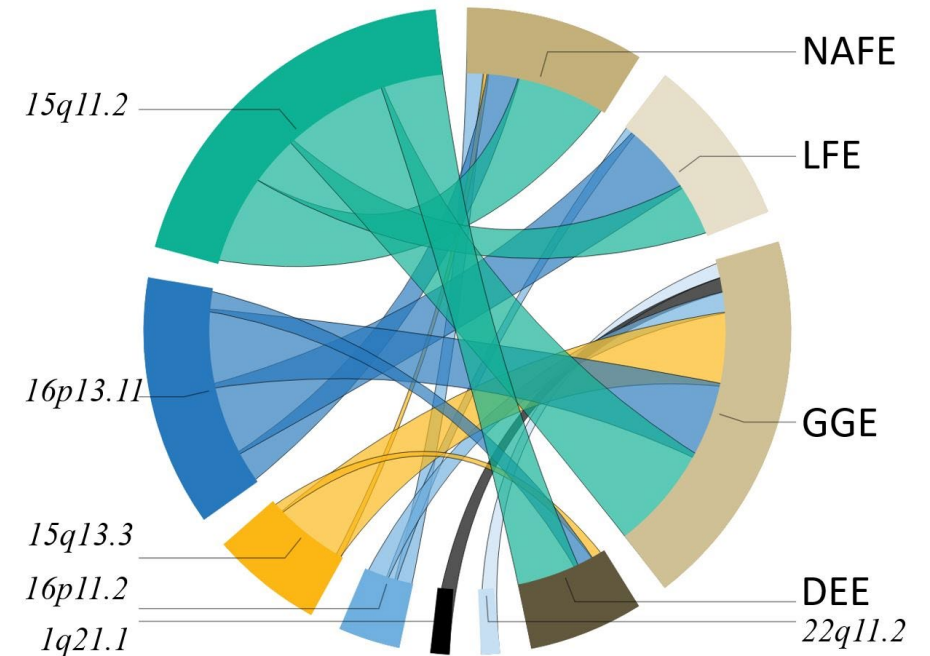
Article

<https://doi.org/10.1038/s41467-023-39539-6>

Genome-wide identification and phenotypic characterization of seizure-associated copy number variations in 741,075 individuals

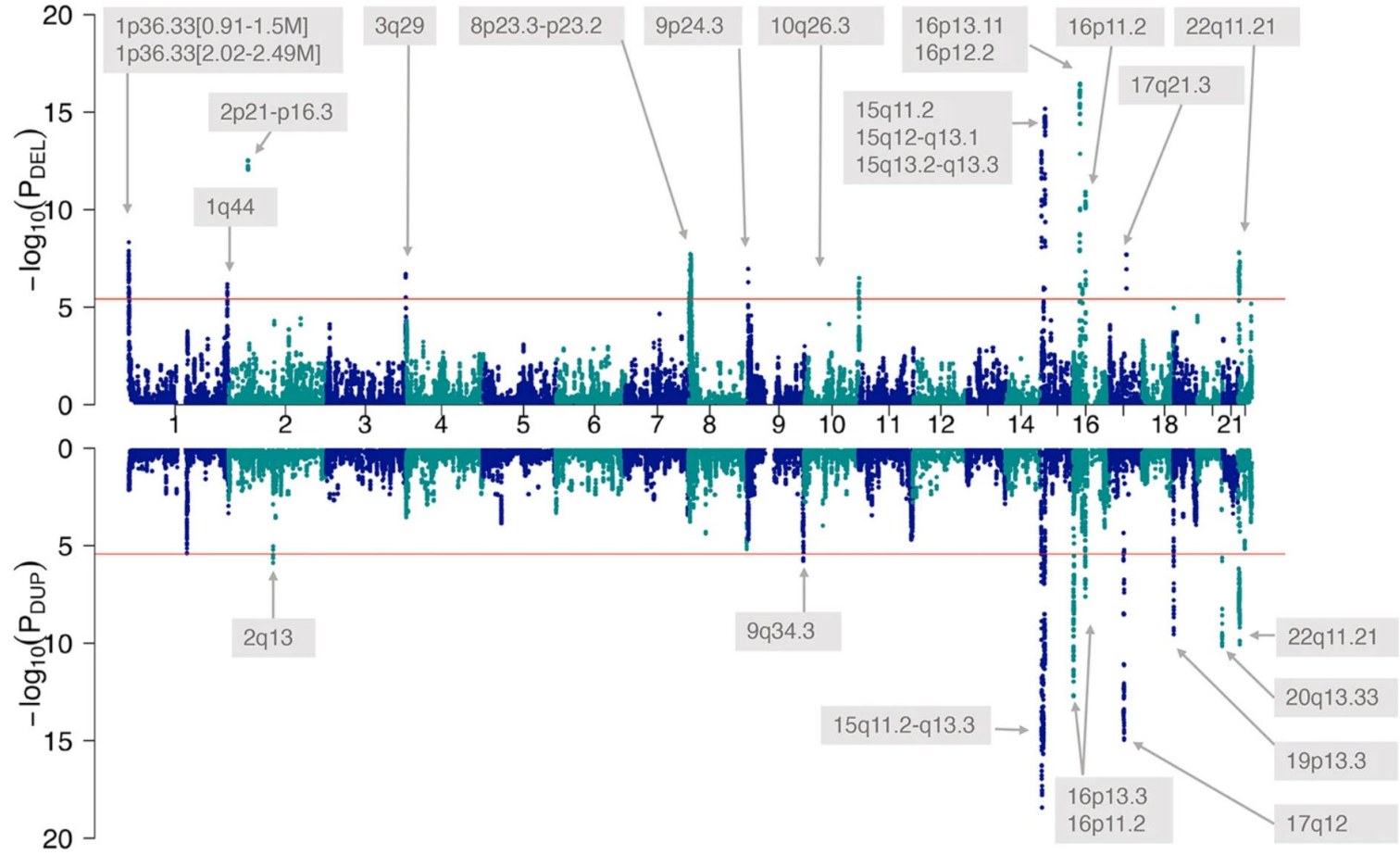
Genome-wide identification and phenotypic characterization of seizure-associated copy number variations in 741,075 individuals

- Ziel der Studie:
 - Signifikanz vieler CNV Befunde unklar
 - Bislang nur 3 signifikante Loci
 - Meta-Analyse von
 - › 26.699 Individ mit Epilepsie/Anfällen
 - › 492.324 Kontrollen
 - › 248.751 neuropsychiatrische Erkrankungen

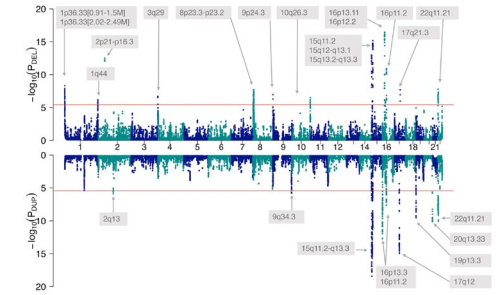
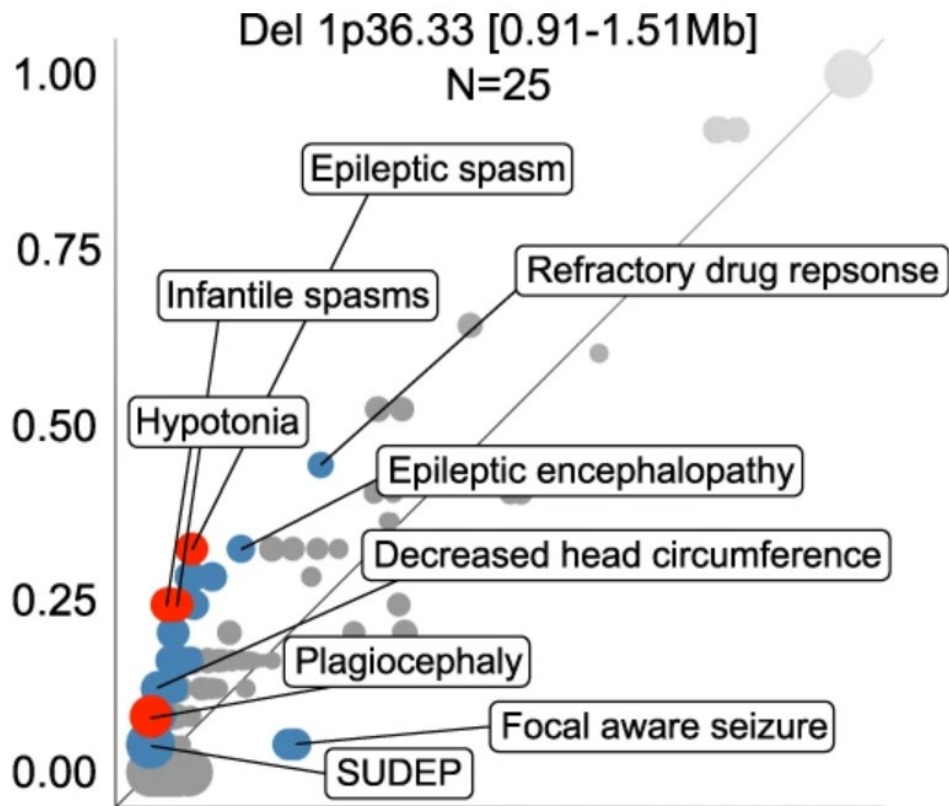
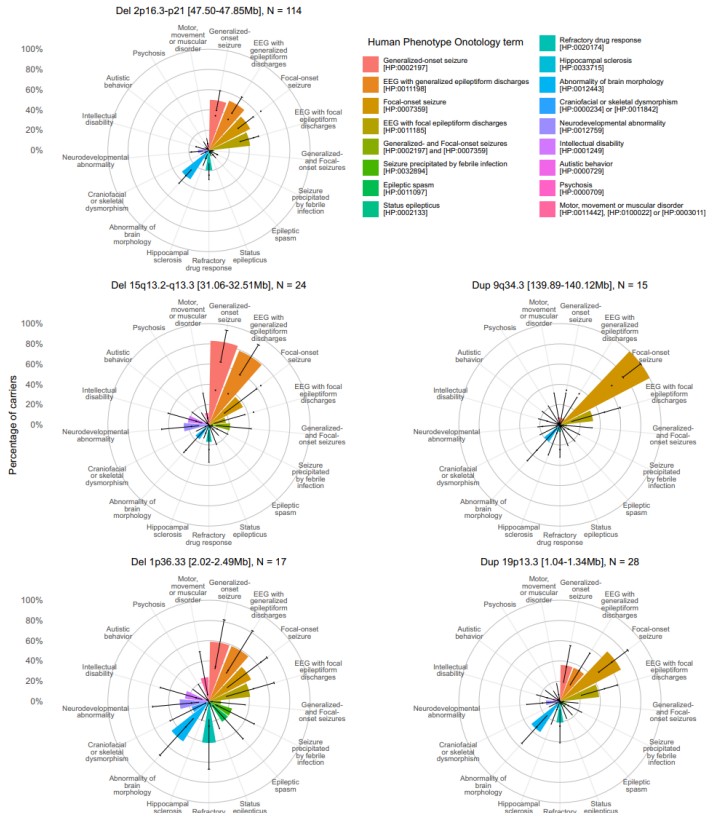


based on data from Niestroj et al. 2020

Genome-wide identification and phenotypic characterization of seizure-associated copy number variations in 741,075 individuals

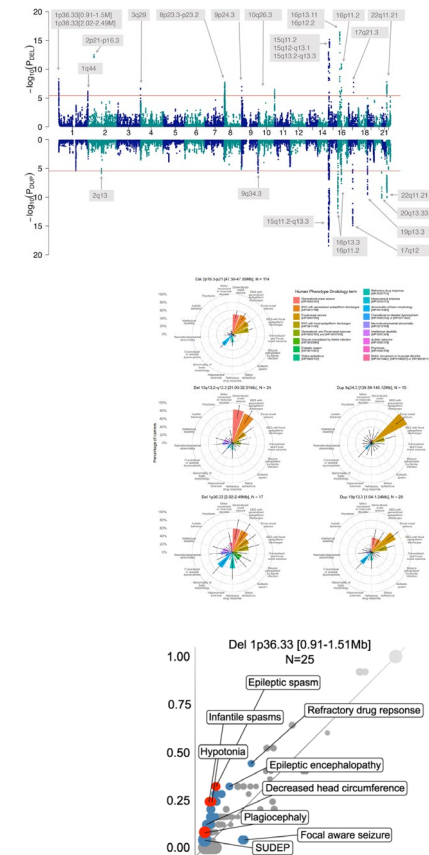


Genome-wide identification and phenotypic characterization of seizure-associated copy number variations in 741,075 individuals



Genome-wide identification and phenotypic characterization of seizure-associated copy number variations in 741,075 individuals

- Die Studie beweist die Relevanz von CNVs als Risiko-faktoren für Epilepsie
- Sie zeigt erneut, dass Epilepsie aufgrund eines “Ungleichgewichts” im Gehirn steht, durch den Nachweis von Epilepsiesyndromen bei Duplikationen und Deletionen vieler identischer Regionen
- Die Studie versucht eine phänotypische Kartografie innerhalb der Grenzen seltener Erkrankungen



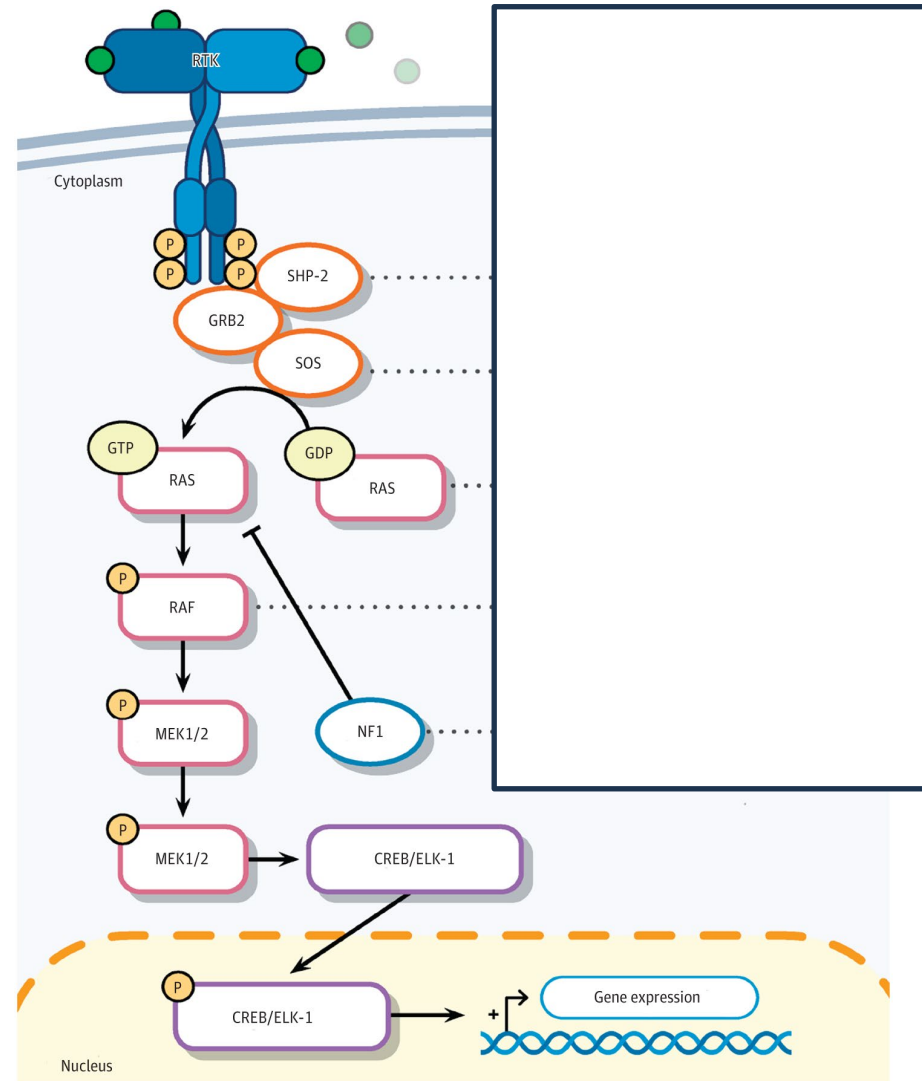
Was hat die Neurofibromatose 1 mit der Temporallappenepilepsie Erwachsener zu tun?

JAMA Neurology | **Original Investigation**

Contribution of Somatic Ras/Raf/Mitogen-Activated Protein Kinase Variants in the Hippocampus in Drug-Resistant Mesial Temporal Lobe Epilepsy

Sattar Khoshkhoo, MD; Yilan Wang, BS; Yasmine Chahine, BS; E. Zeynep Erson-Omay, PhD; Stephanie M. Robert, MD, PhD; Emre Kiziltug, BS; Eyiyemisi C. Damisah, MD; Carol Nelson-Williams, MS; Guangya Zhu, PhD; Wenna Kong, BS; August Yue Huang, PhD; Edward Stronge, BS; H. Westley Phillips, MD; Brian H. Chhouk, BS; Sara Bizzotto, PhD; Ming Hui Chen, MD, MMSc; Thiuni N. Adikari, BMSc; Zimeng Ye, MS; Tom Witkowski, BSc; Dulcie Lai, PharmD, PhD; Nadine Lee; Julie Lokan, MBBS; Ingrid E. Scheffer, MBBS, PhD; Samuel F. Berkovic, MD; Shozeb Haider, PhD; Michael S. Hildebrand, PhD; Edward Yang, MD, PhD; Murat Gunel, MD; Richard P. Lifton, MD, PhD; R. Mark Richardson, MD, PhD; Ingmar Blümcke, MD; Sanda Alexandrescu, MD; Anita Huttner, MD; Erin L. Heinzen, PharmD, PhD; Jidong Zhu, PhD; Annapurna Poduri, MD, MPH; Nihal DeLanerolle, DPhil, DSc; Dennis D. Spencer, MD; Eunjung Alice Lee, PhD; Christopher A. Walsh, MD, PhD; Kristopher T. Kahle, MD, PhD

Contribution of Somatic Ras/Raf/Mitogen-Activated Protein Kinase Variants in the Hippocampus in Drug-Resistant Mesial Temporal Lobe Epilepsy



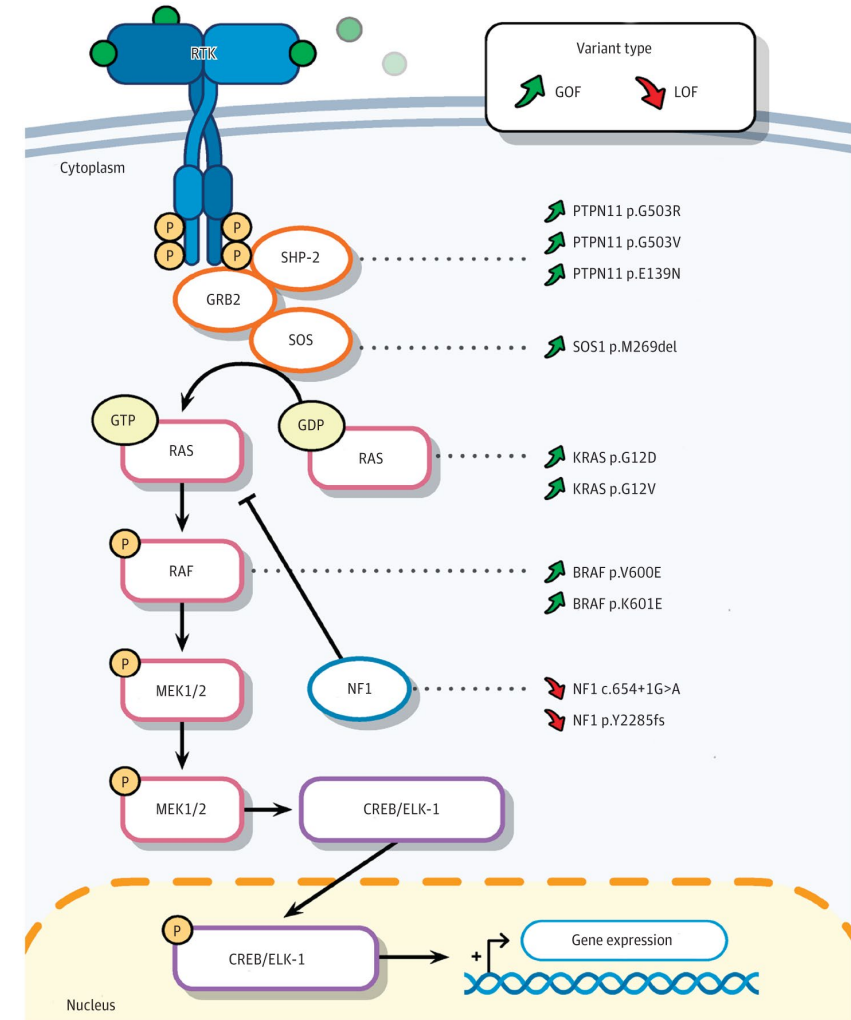
Contribution of Somatic Ras/Raf/Mitogen-Activated Protein Kinase Variants in the Hippocampus in Drug-Resistant Mesial Temporal Lobe Epilepsy

Table. Pathogenic Somatic Variants in Mesial Temporal Lobe Epilepsy

Patient No./sex/age at surgery, y	Clinical diagnosis	Gene	Variant coordinates	Protein change	VAF, %	
					Sequencing (validation) in the hippocampus	Validation in the temporal neocortex
1/Male/30s	MTS	<i>PTPN11</i>	NM_002834.5: c.1507G>A	p.G503R	2.4 (1.4-1.5)	<0.2
2/Male/30s	MTS with LEAT	<i>PTPN11</i>	NM_002834.4: c.1508G>T	p.G503V	2.9 (2.1-2.5)	<0.2
3/Male/20s	MTS	<i>PTPN11</i>	NM_002834.5: c.417G>C	p.E139N	3.3 (3.3)	0.8-0.9
4/Male/20s	MTS	<i>NF1</i>	NM_001042492.3: c.654 + 1G>A; germline NM_001042492.3: c.499_502del	Altered splicing p.C167fs	2.2 (2.0)	0.9
5/Female/20s	MTS with LEAT	<i>NF1</i>	NM_001042492.3: c.6852-6855del; germline NM_001042492.3: c.6904C>T	p.Y2285fs p.Q2302*	6.3 (6.3)	NA
6/Male/40s	MTS	<i>KRAS</i>	NM_004985.5: c.35G>A	p.G12D	1.2 (0.9-0.9)	<0.2
7/Male/<10	MTS with FCD1A	<i>KRAS</i>	NM_004985.5: c.35G>T ^a	p.G12V	19.6 (18)	NA
8/Female/50s	MTS	<i>SOS1</i>	NM_005633.4: c.810-813del	p.M269del	1.2 (0.52-0.88)	0.6
9/Female/10s	MTS with LEAT	<i>BRAF</i>	NM_004333.6: c.1799T>A	p.V600E	7.9 (7.82-7.9)	NA
10/Male/<10	MTS with FCD2A	<i>BRAF</i>	NM_004333.6: c.1797A>G	p.K601E	31.3 (17.8)	8.8
11/Female/50s	MTS	<i>SF3B1</i>	NM_012433.3: c.2098A>G	p.K700E	1.7 (1.5-1.7)	<0.2

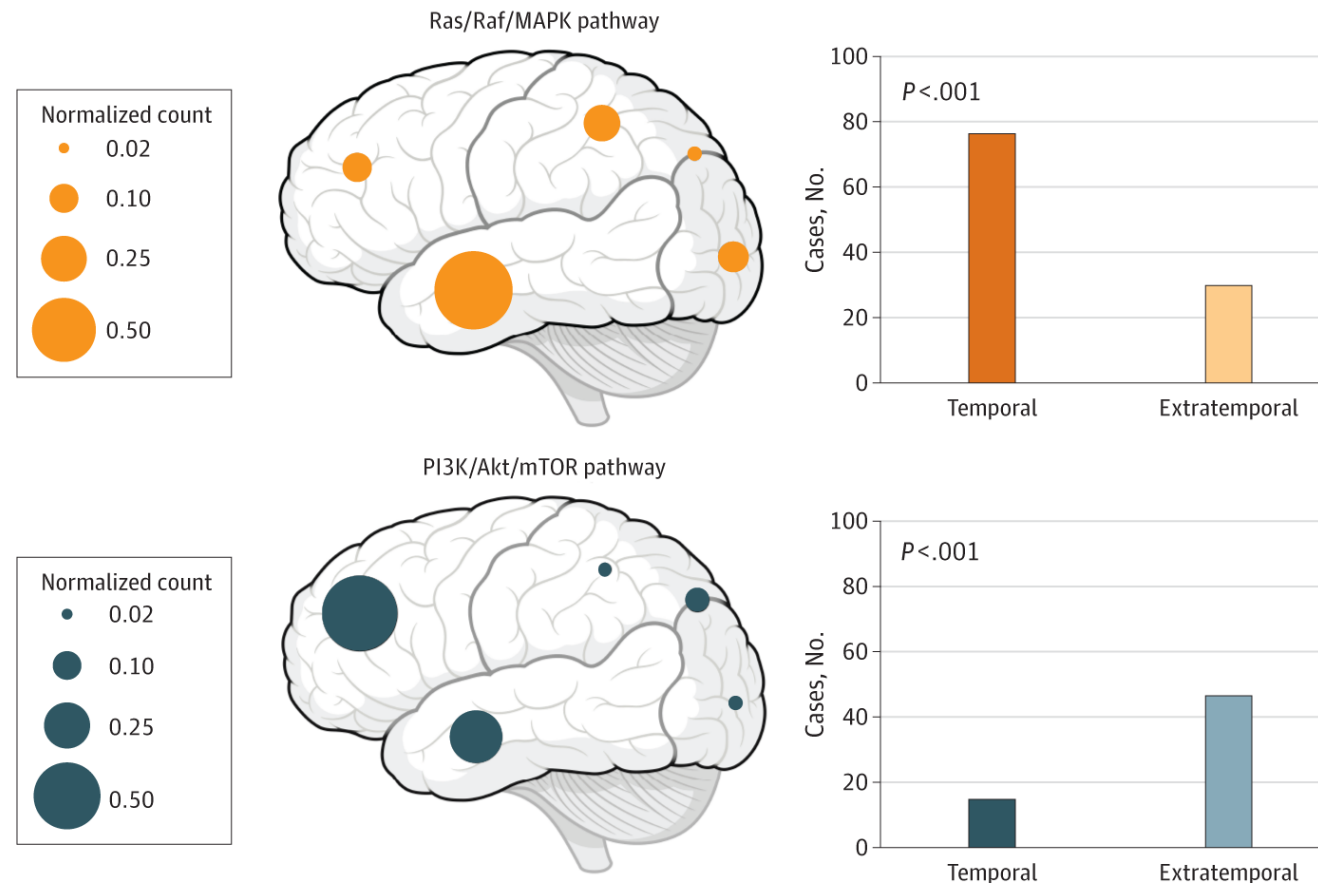
Abbreviations: FCD, focal cortical dysplasia; LEAT, low-grade epilepsy-associated tumor; MTS, mesial temporal sclerosis; NA, not available; VAF, variant allele frequency.

^a Has been previously reported in a separate cohort consisting of malformations of cortical development.²³



Contribution of Somatic Ras/Raf/Mitogen-Activated Protein Kinase Variants in the Hippocampus in Drug-Resistant Mesial Temporal Lobe Epilepsy

A Ras/Raf/MAPK and PI3K/Akt/mTOR pathway variants



- Die Studie zeigt, dass auch der Ras-MAPKinase Weg direkt in die Epilepsie-Entstehung involviert ist
- Ähnlich zu MTOR-Signalweg Mosaiken, finden sich v.a. bei der Temporallappenepilepsie Mutationen im Gewebe
- Die Studie zeigt die Relevanz wichtiger Signalwege bei der Entstehung globaler und lokaler neuronaler Dysfunktion

Kann man Medikamente, Elektrostimulation und Epilepsiechirurgie vergleichen?


ARTICLES | [VOLUME 7, ISSUE 7, P455-462, JULY 2023](#)

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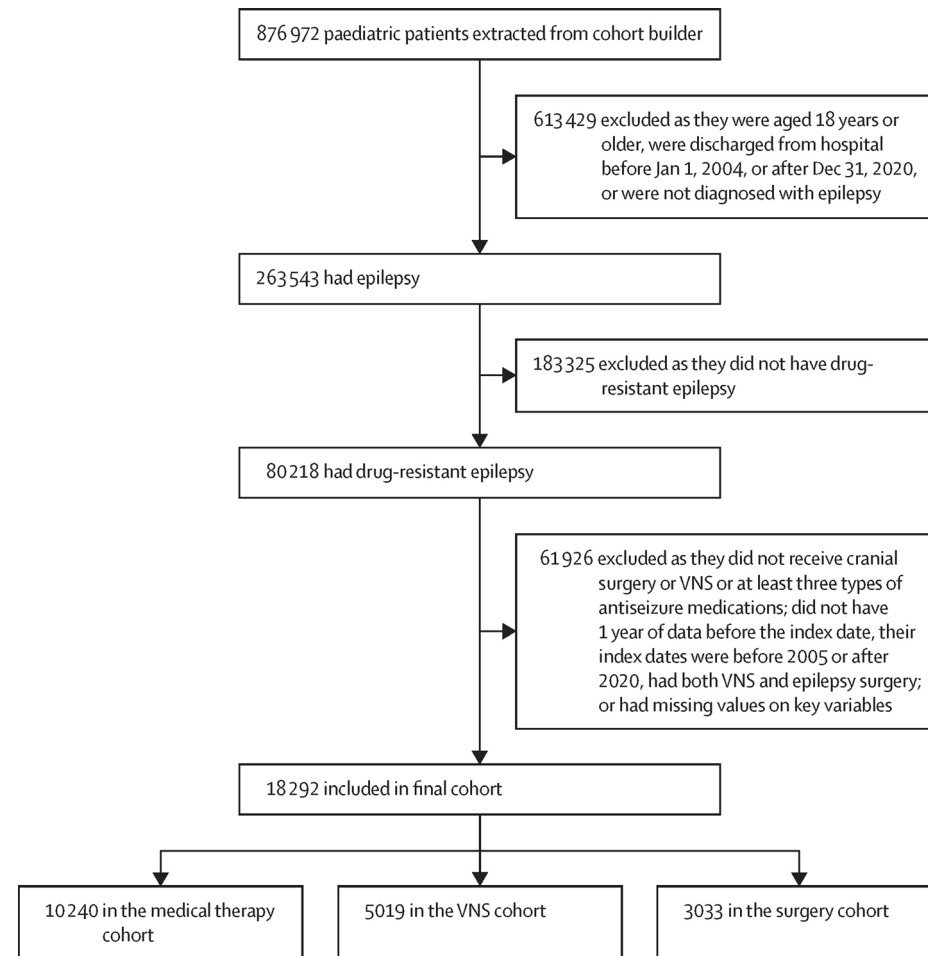
Comparison of long-term survival with continued medical therapy, vagus nerve stimulation, and cranial epilepsy surgery in paediatric patients with drug-resistant epilepsy in the USA: an observational cohort study

[Lu Zhang, PhD](#) • [Matt Hall, PhD](#) • [Prof Sandi K Lam, MD](#)  

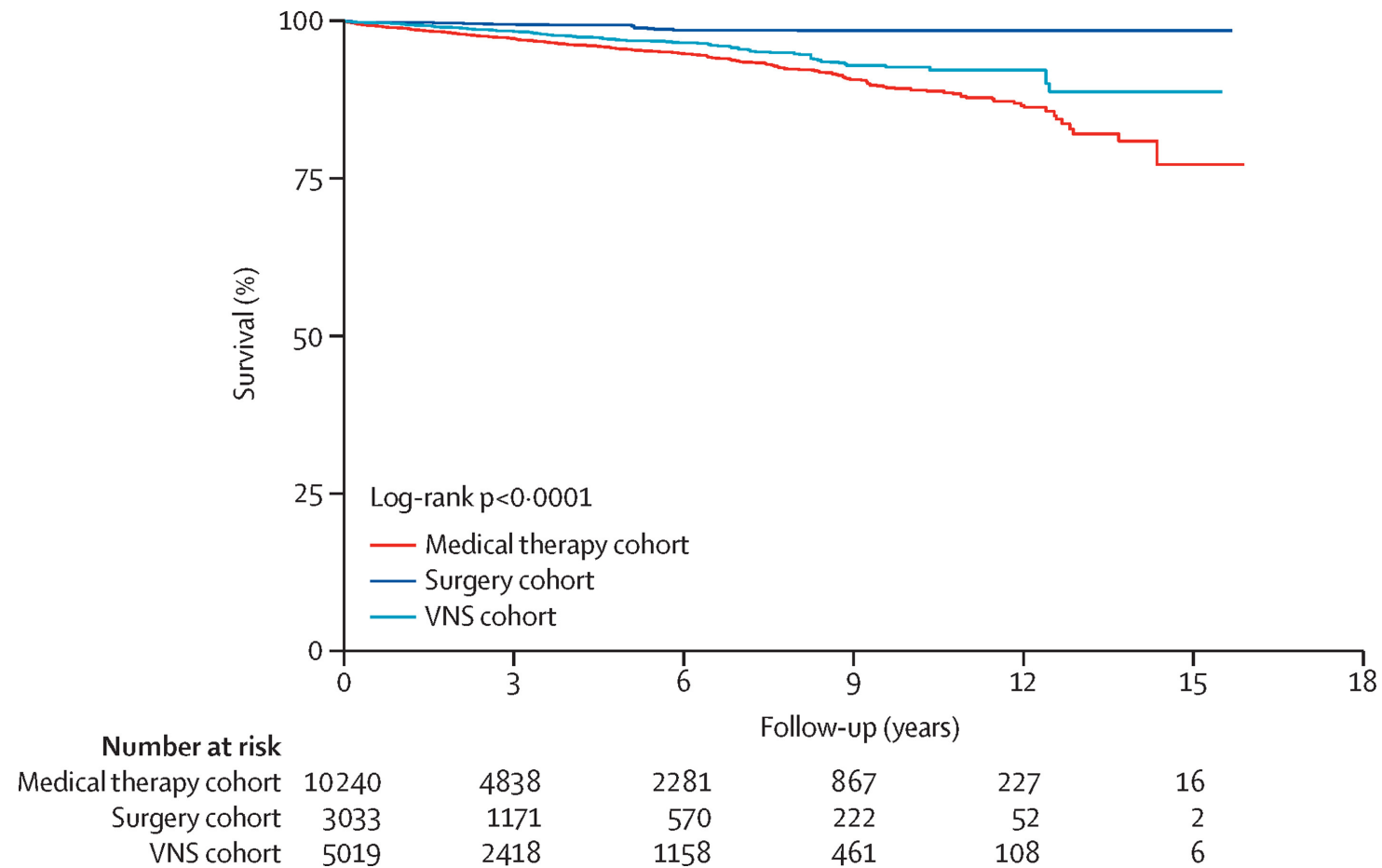
Published: June 02, 2023 • DOI: [https://doi.org/10.1016/S2352-4642\(23\)00082-2](https://doi.org/10.1016/S2352-4642(23)00082-2) •

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Long-term survival with continued medical therapy, vagus nerve stimulation, and cranial epilepsy surgery in paediatric patients



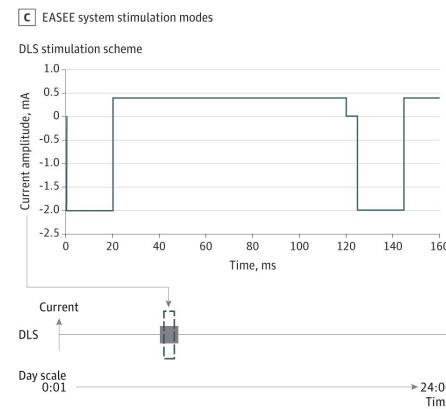
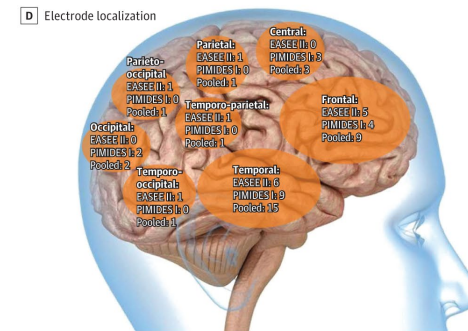
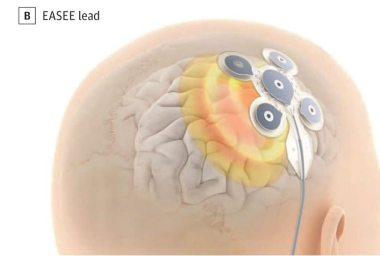
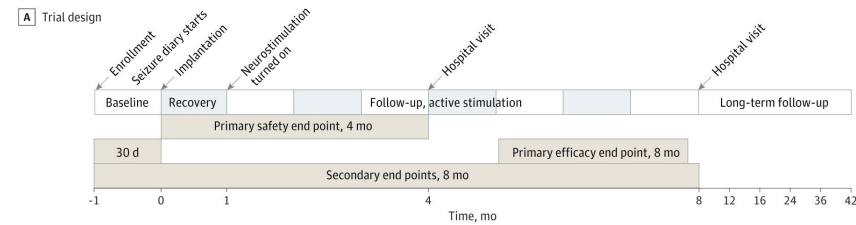
Long-term survival with continued medical therapy, vagus nerve stimulation, and cranial epilepsy surgery in paediatric patients



- Epilepsiechirurgie hat die besten LZ-Ergebnisse für den Endpunkt “Überleben”
- VNS als Elektrostimulation war ebenfalls mit einem besseren LZ-Überleben assoziiert

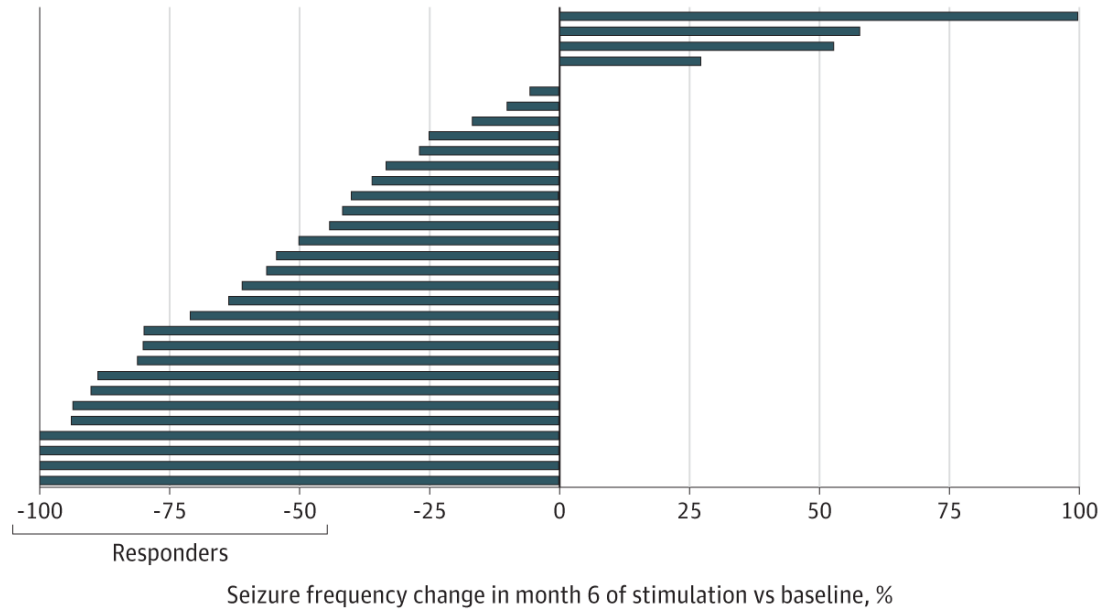
Helfen neue Verfahren der Elektrostimulation bei Epilepsie?

Focal Cortex Stimulation With a Novel Implantable Device and Antiseizure Outcomes in 2 Prospective Multicenter Single-Arm Trials

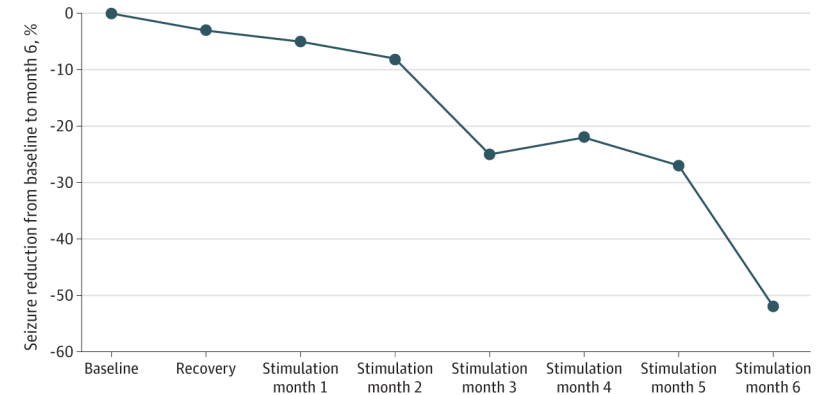


Focal Cortex Stimulation With a Novel Implantable Device and Antiseizure Outcomes in 2 Prospective Multicenter Single-Arm Trials

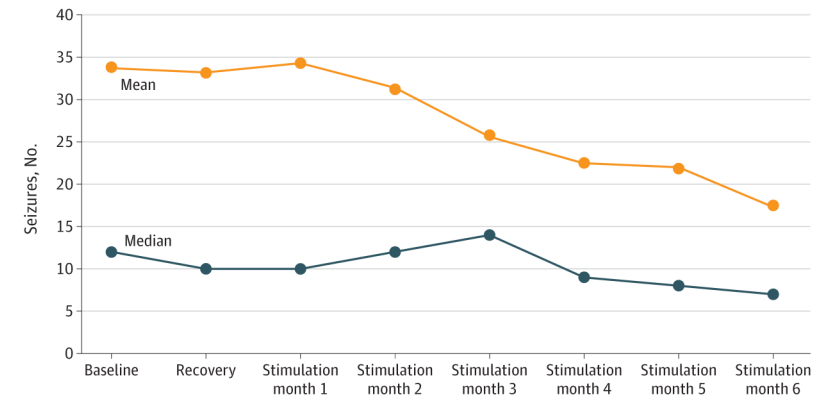
A Change in seizure frequency at month 6 vs baseline



B Median percentage reduction in seizure frequency



C Mean and median seizure frequency



- Auch die transkranielle Fokusstimulation scheint eine Therapieoption für fokale Epilepsie zu sein
- Aktuell hat die Studie bei Kindern, 12-17 Jahre alt begonnen – bei Interesse, bitte melden.

Neue versus alte Biomarker im EEG

High Frequency Oscillations in der Praxis

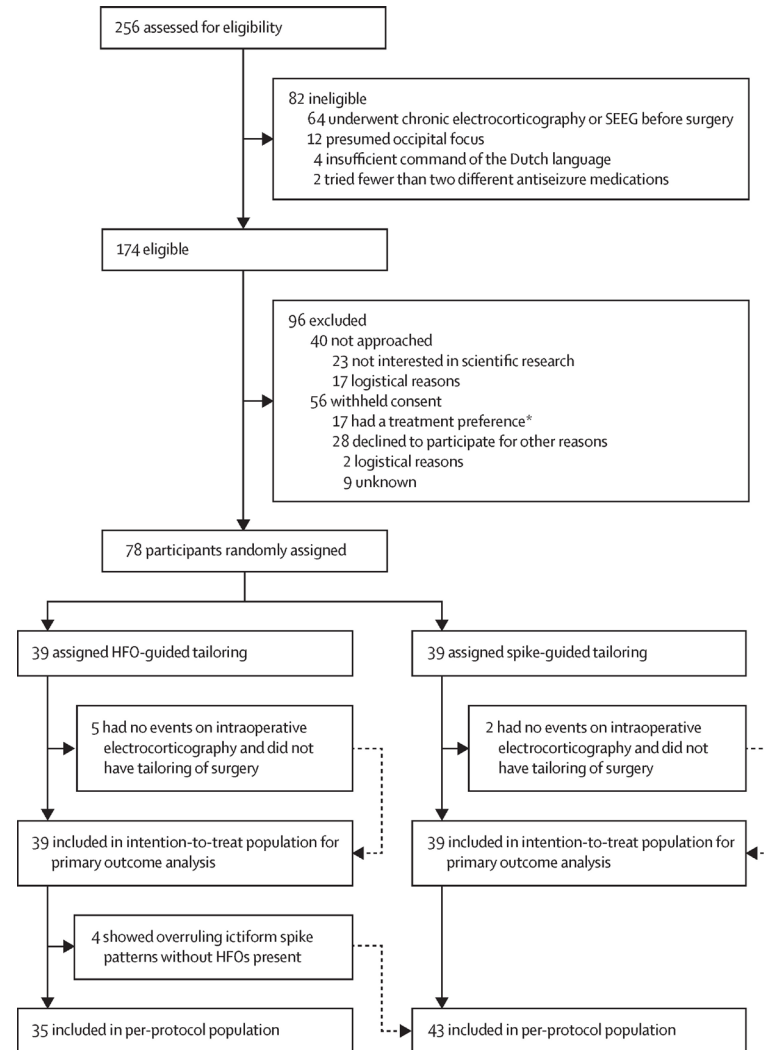
ARTICLES | [VOLUME 21, ISSUE 11, P982-993, NOVEMBER 2022](#)

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Intraoperative electrocorticography using high-frequency oscillations or spikes to tailor epilepsy surgery in the Netherlands (the HFO trial): a randomised, single-blind, adaptive non-inferiority trial

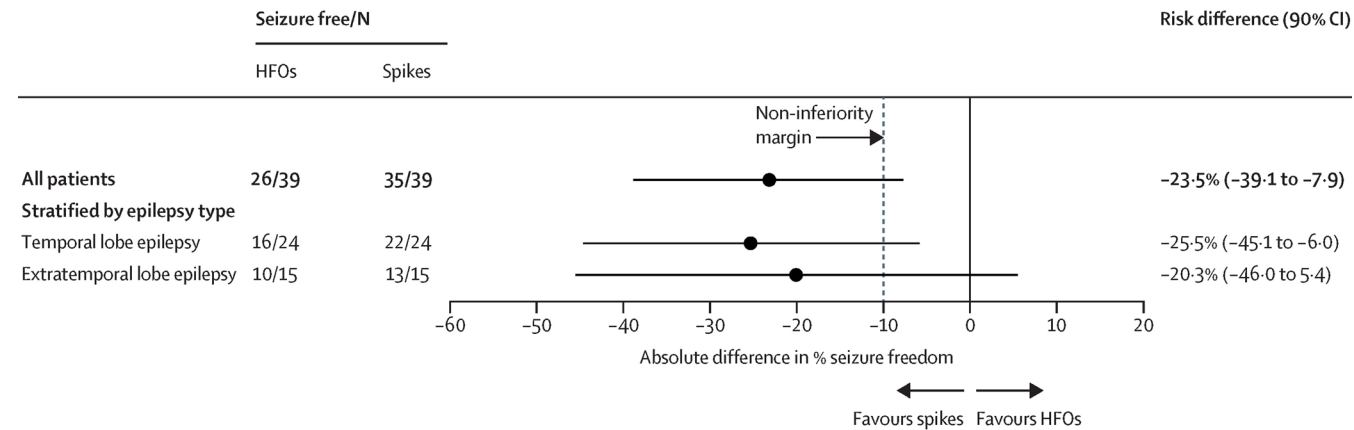
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Neue versus alte Biomarker im EEG

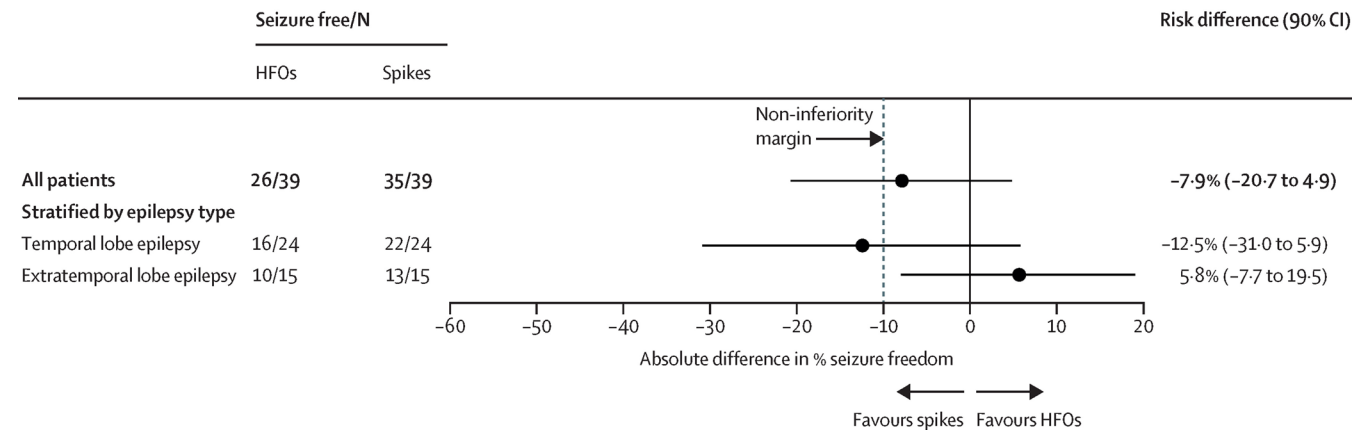


Neue versus alte Biomarker im EEG

A Intention-to-treat analysis



B After correcting for confounding by poor pathology prognosis





























- HFOs sind **nicht** “nicht-schlechter” als Spikes im intraoperativen EEG
- In einer ersten prospektiven Studie bestätigen sich die Hoffnungen in ‘HFOs’ als einen besseren EEG-Marker nicht wider

Welche Daten brauchen wir bei seltenen Erkrankungen um Studien durchzuführen?

August 29, 2023; 101 (9) **RESEARCH ARTICLE**

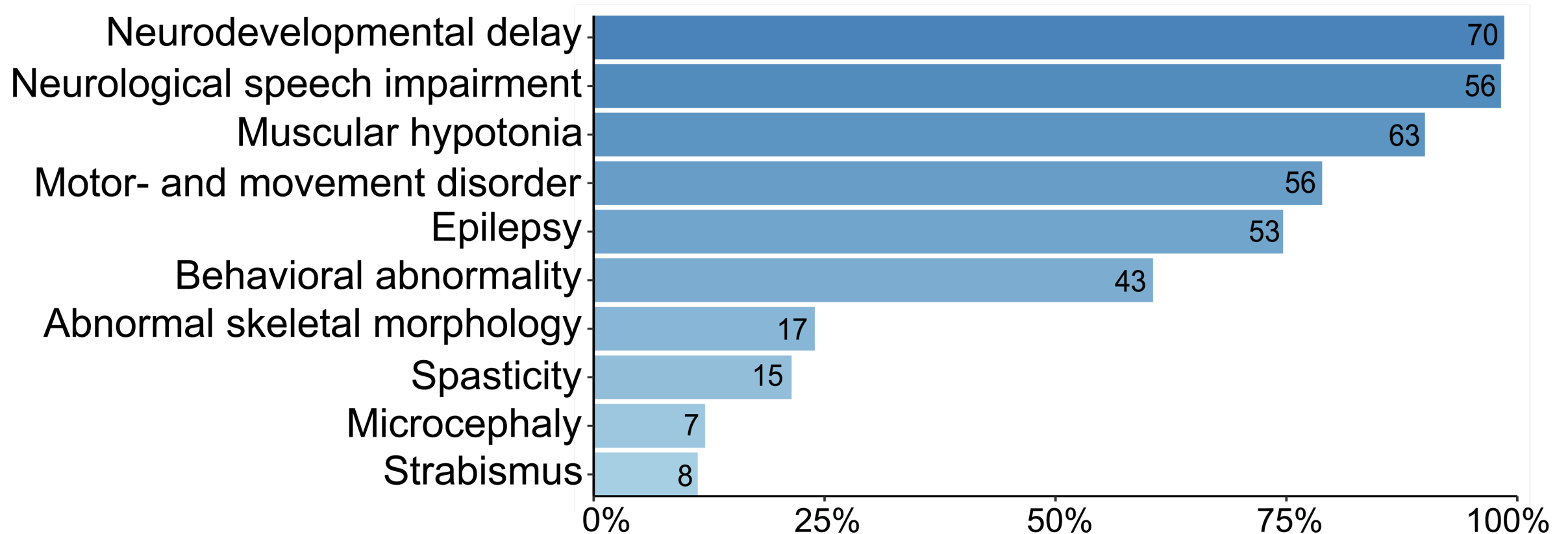
Natural History and Developmental Trajectories of Individuals With Disease-Causing Variants in *STXBP1*

 Kim M. Thalwitzer,  Jan H. Driedger,  Julie Xian,  Afshin Saffari,  Pia Zacher,  Bigna K. Bölsterli, Sarah McKeown Ruggiero,  Katie Rose Sullivan,  Alexandre N. Datta,  Christoph Kellinghaus, Jürgen Althaus,  Adelheid Wiemer-Kruel,  Andreas van Baalen, Armin Pampel, Michael Alber,  Hilde M.H. Braakman, Otfried M. Debus, Jonas Denecke,  Elke Hobbiebrunken, Ina Breitweg, Danielle Diehl, Hans Eitel,  Janina Gburek-Augustat, Martin Preisel, Jan-Ulrich Schlump, Mirjam Laufs,  Dilbar Mammadova, Carsten Wurst,  Christine Prager, Christa Löhr-Nilles, Peter Martin,  Sven F. Garbade,  Konrad Platzer, Ira Benkel-Herrenbrueck, Kerstin Egler, Walid Fazeli,  Johannes R. Lemke, Eva Runkel, Barbara Klein,  Tobias Linden, Julian Schröter, Heike Steffek, Bastian Thies, Florian von Deimling, Sabine Illsinger,  Ingo Borggraefe, Georg Classen,  Dagmar Wieczorek,  Georgia Ramantani,  Stefan Koelker, Georg F. Hoffmann,  Markus Ries,  Ingo Helbig, Steffen Syrbe

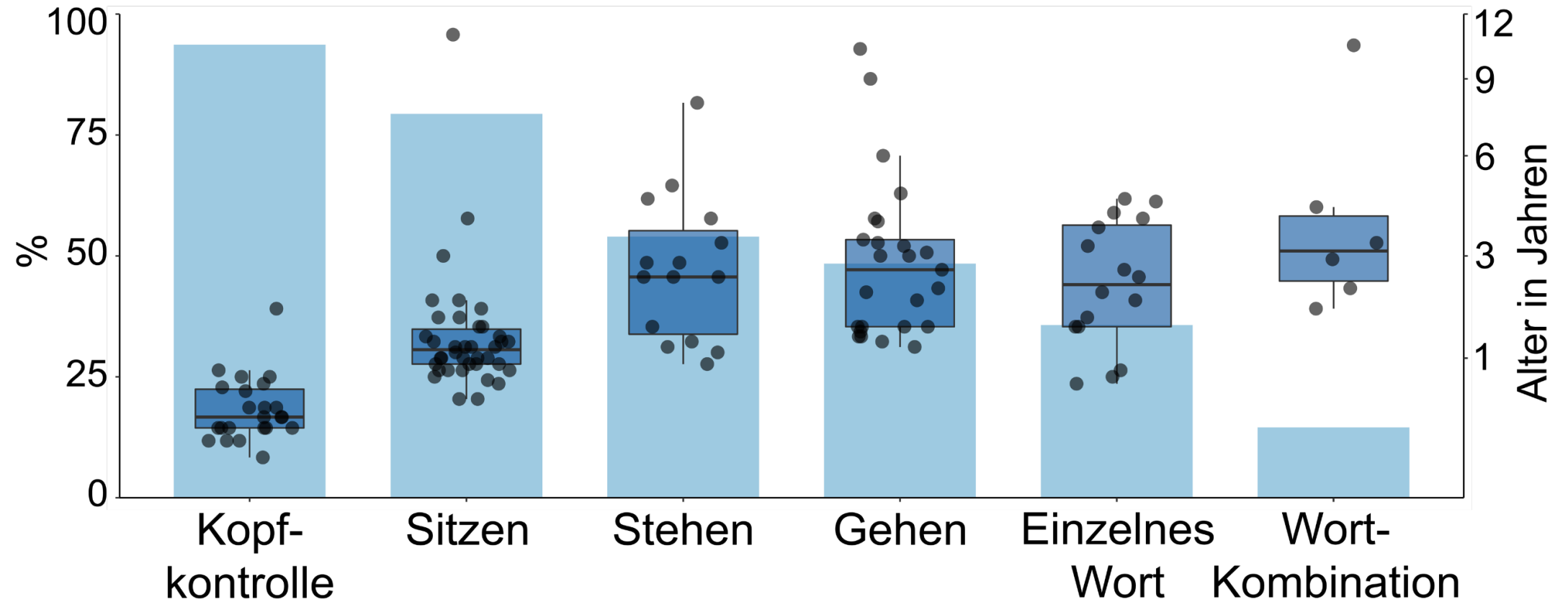
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Neurology Aug 2023, 101 (9) e879-e891

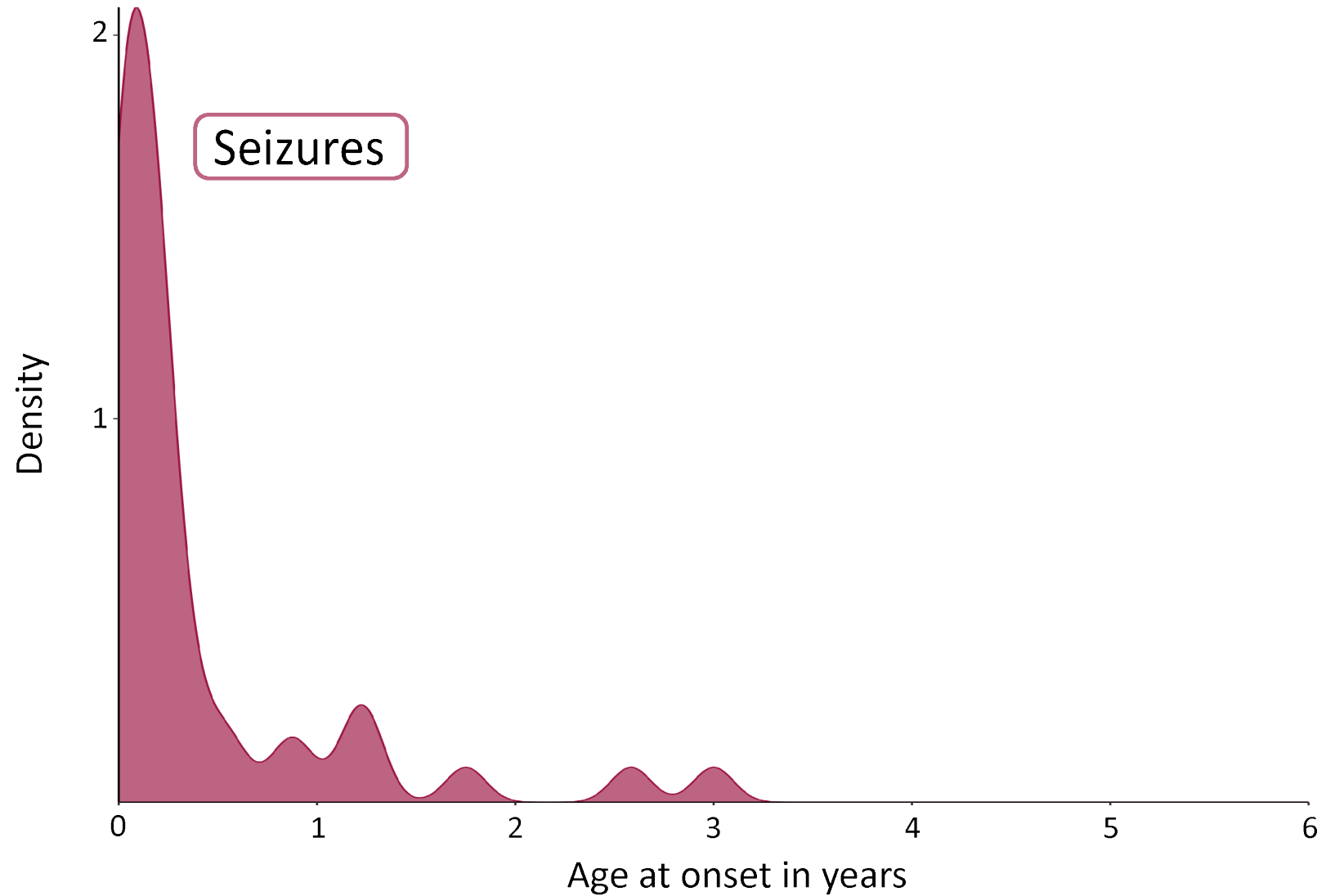
Natural History and Developmental Trajectories of Individuals With Disease-Causing Variants in STXBP1



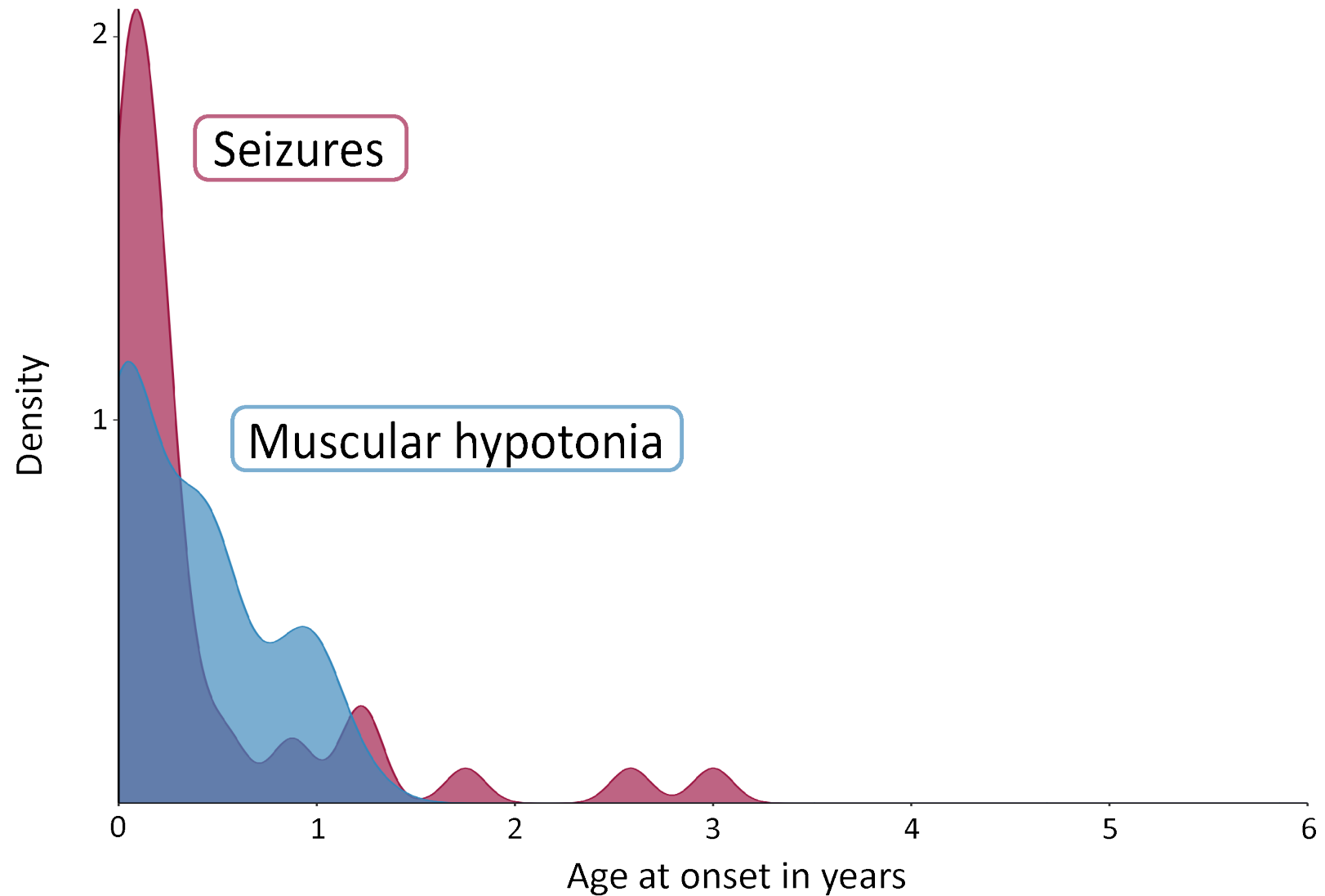
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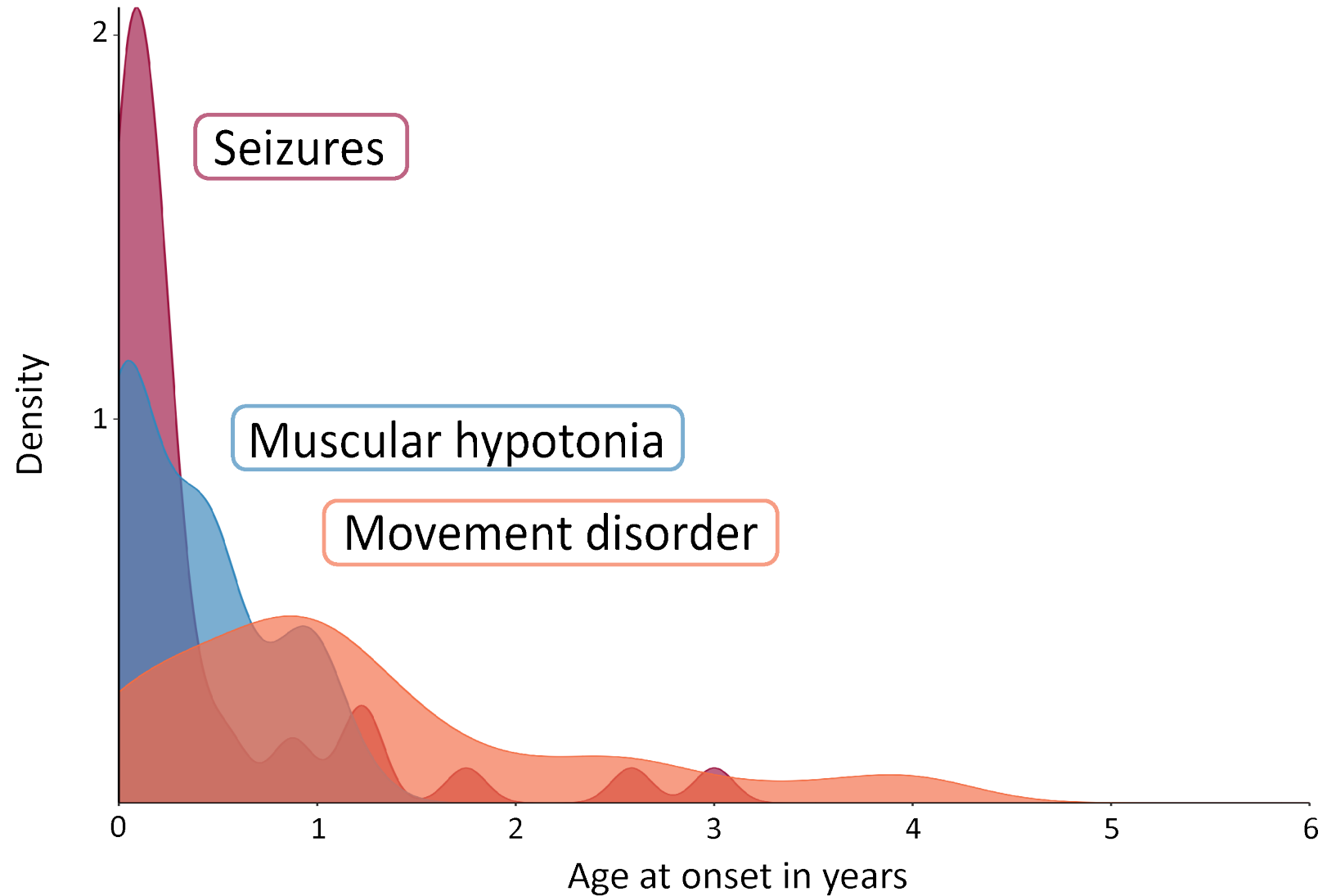
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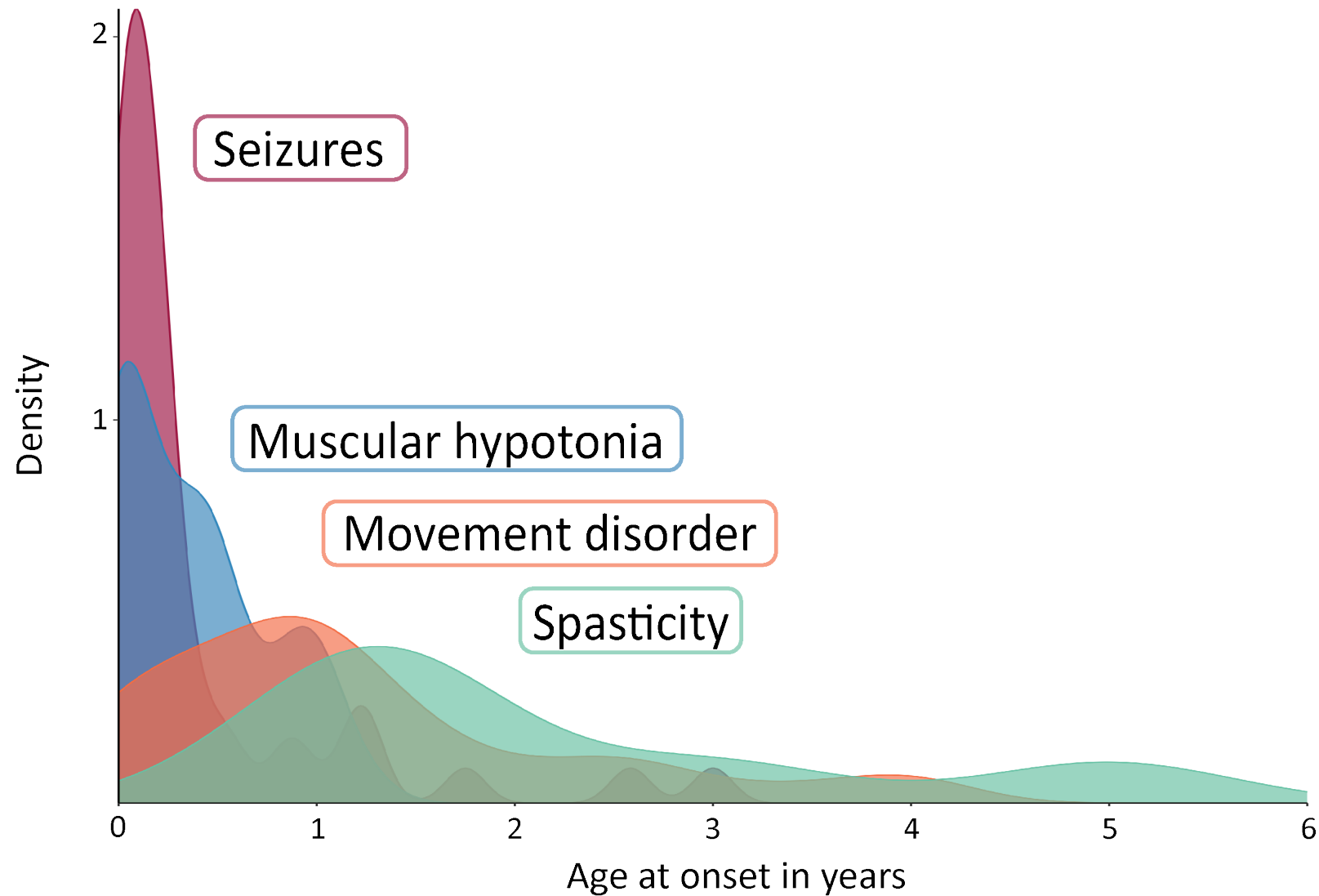
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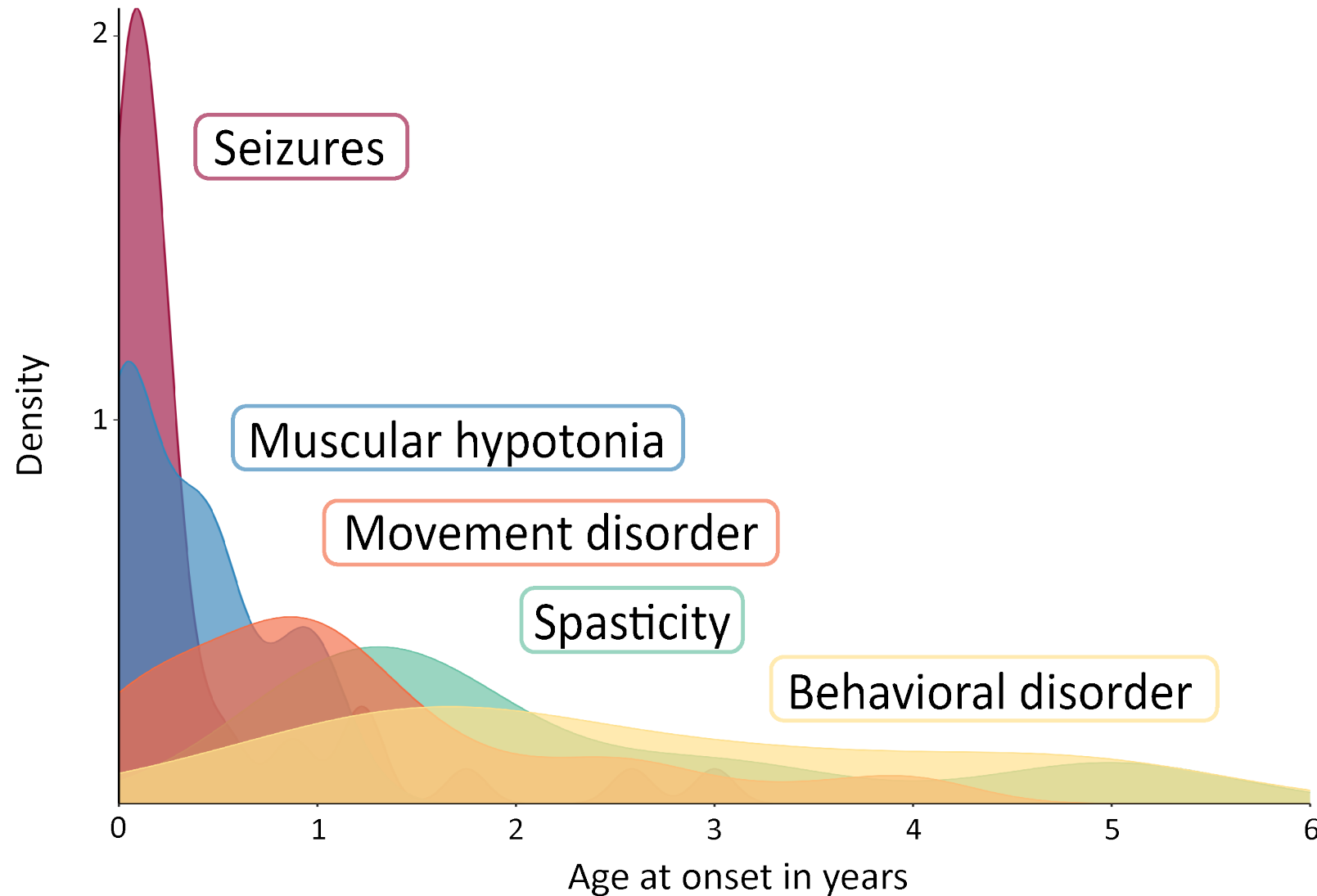
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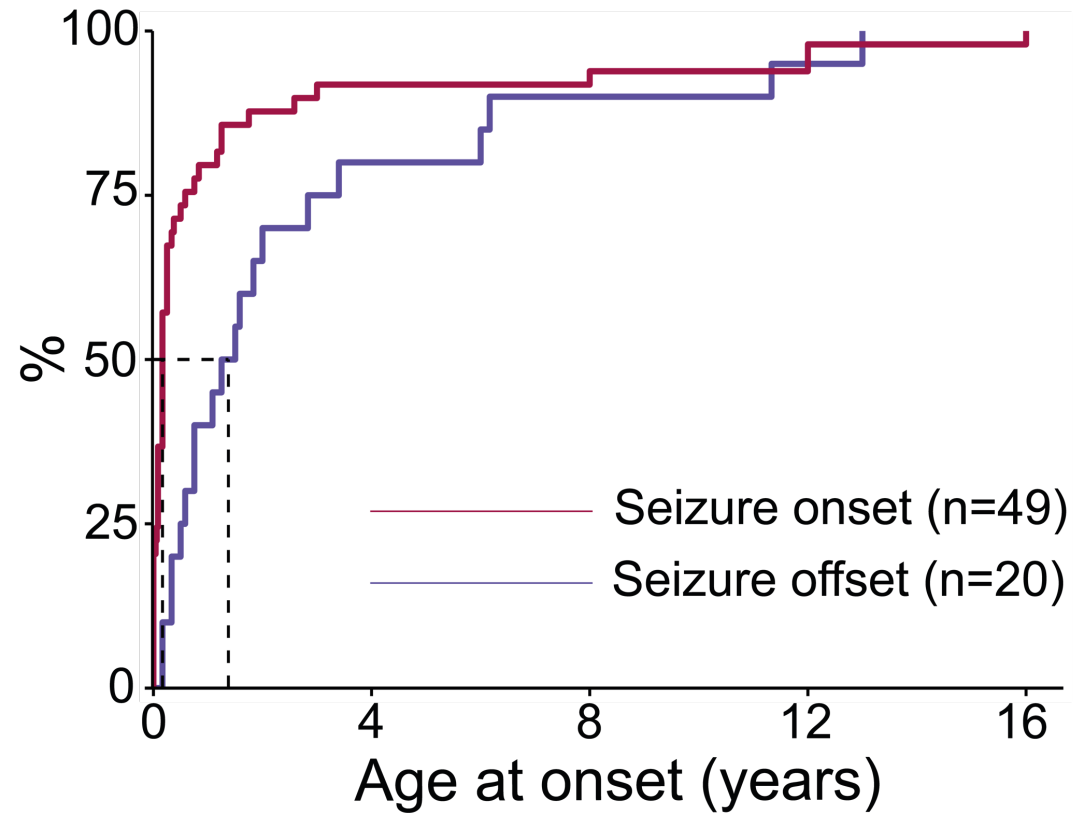
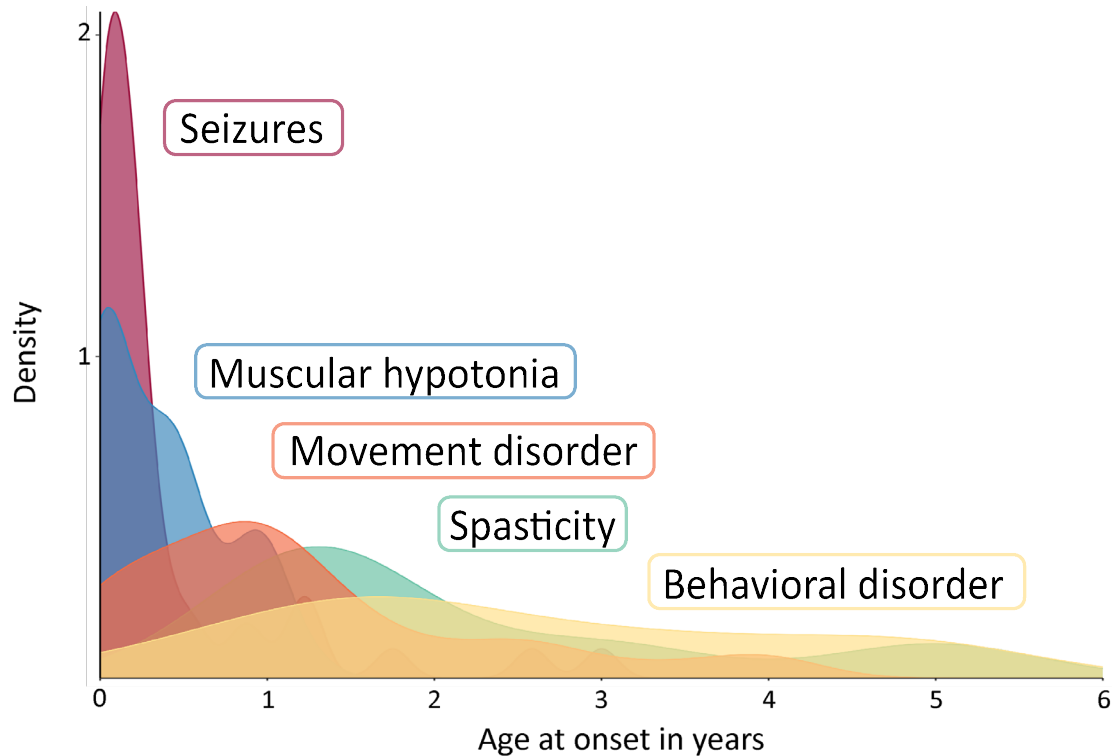
Natural History and Developmental Trajectories of Individuals With Disease-Causing Variants in STXBP1



Natural History and Developmental Trajectories of Individuals With Disease-Causing Variants in STXBP1



Natural History and Developmental Trajectories of Individuals With Disease-Causing Variants in STXBP1



- Nationale Kooperation und Einbindung der Selbsthilfevereine ermöglicht ausreichend große Studien zum Erkrankungsverlauf
- Natural History Studien können quantifizierbare Endpunkte außerhalb der Epilepsie für Therapiestudien bei DEEs definieren

Danke

Kontaktinformationen

Sollten wir Ihr Interesse für eine Teilnahme geweckt haben, oder Sie weitere Informationen wünschen, sprechen Sie gerne Ihren behandelnden Arzt direkt an.

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Neue Studie bei Neugeborenen und jungen Säuglingen mit tuberöser Sklerose

Neuropsychologische Langzeit-Entwicklung von präventiv mit mTOR-Inhibitoren behandelten Kindern im Vergleich zur Standardbehandlung bei Kindern mit tuberöser Sklerose unter 4 Monaten



Henje Driedger, Afshin Saffari, Julian Schröter, Annick Klabunde, Laura Orec, Elisabeth Schuler, MTA der Epileptologie (Heiko, Anett, Tobias)Doktorandinnen (**Kim Thalwitzer**, Prisca Wille, Carolin Fruh, Ben Sonnek, Oliver Urban), Tuberöse Sklerose Deutschland e.V. und Tuberöse Sklerose Stiftung Deutschland, BMBF

Antisense oligonucleotide therapy for *KCNT1* encephalopathy

Liseth Estefania Burbano,¹ Melody Li,¹ Nikola Jancovski,¹ Paymaan Jafar-Nejad,² Kay Richards,¹ Alicia Sedo,¹ Armand Soriano,² Ben Rollo,¹ Linghan Jia,¹ Elena V. Gazina,¹ Sandra Piltz,³ Fatwa Adikusuma,³ Paul Q. Thomas,^{3,4} Helen Kopsidas,¹ Frank Rigo,² Christopher A. Reid,¹ Snezana Maljevic,¹ and Steven Petrou^{1,5}

¹The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Victoria, Australia.
















²Ionis Pharmaceuticals, Carlsbad, California, USA. ³School of Medicine, University of Adelaide, Adelaide, South Australia, Australia. ⁴South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia. ⁵Praxis Precision Medicines, Cambridge, Massachusetts, USA.

HOME > SCIENCE TRANSLATIONAL MEDICINE > VOL. 15, NO. 688 > AN ASO THERAPY FOR ANGELMAN SYNDROME THAT TARGETS AN EVOLUTIONARILY...

 | **RESEARCH ARTICLE** | NEURODEVELOPMENTAL DISEASE



An ASO therapy for Angelman syndrome that targets an evolutionarily conserved region at the start of the *UBE3A-AS* transcript

[SCOTT V. DINDOT](#)  , [SARAH CHRISTIAN](#)  , [WILLIAM J. MURPHY](#)  , [ALLYSON BERENT](#) , [JENNIFER PANAGOULIAS](#)  , [ANNALISE SCHLAFER](#)  , [JOHNATHAN BALLARD](#)  , [KAMELIA RADEVA](#)  , [RUTH ROBINSON](#) , [LUKE MYERS](#)  , [THOMAS JEPP](#)  , [HILLARY SHAHEEN](#)  , [PAUL HILLMAN](#)  , [KRANTI KONGANTI](#) , [ANDREW HILLHOUSE](#)  , [KEVIN R. BREDEMEYER](#)  , [LAUREN BLACK](#)  , [JULIE DOUVILLE](#)  , AND ON BEHALF OF THE FIRE CONSORTIUM

fewer

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Levetiracetam vs Lamotrigine as First-Line Antiseizure Medication in Female Patients With Idiopathic Generalized Epilepsy

New Online

Views **4,603** | Citations **0** | Altmetric **89**

Original Investigation

ONLINE FIRST

October 2, 2023

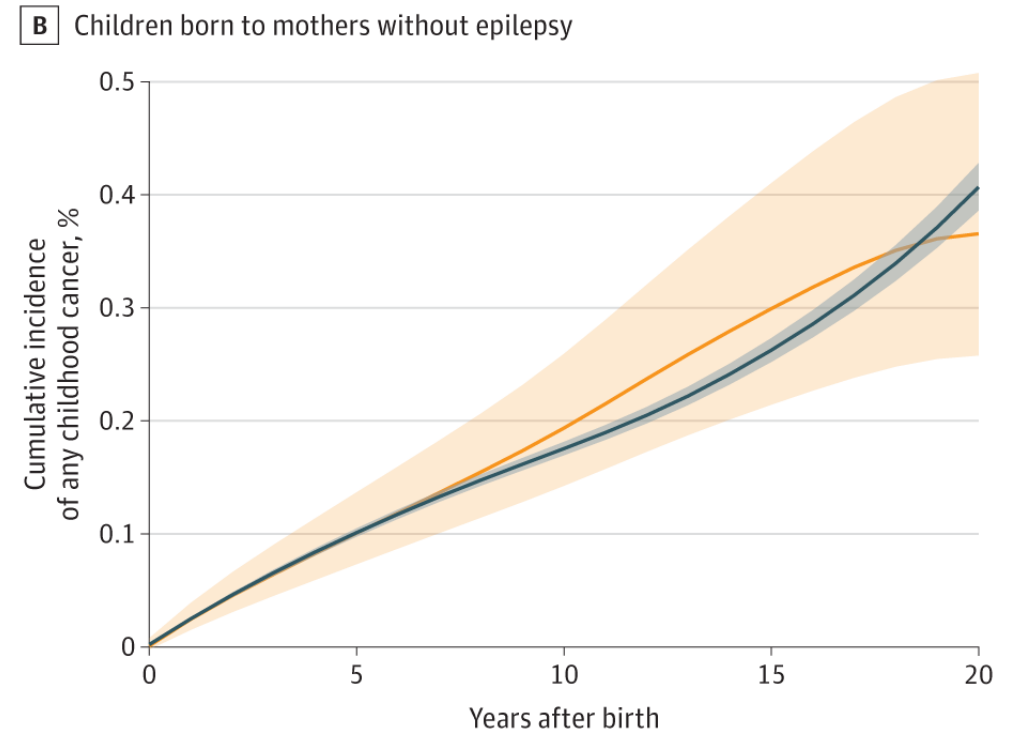
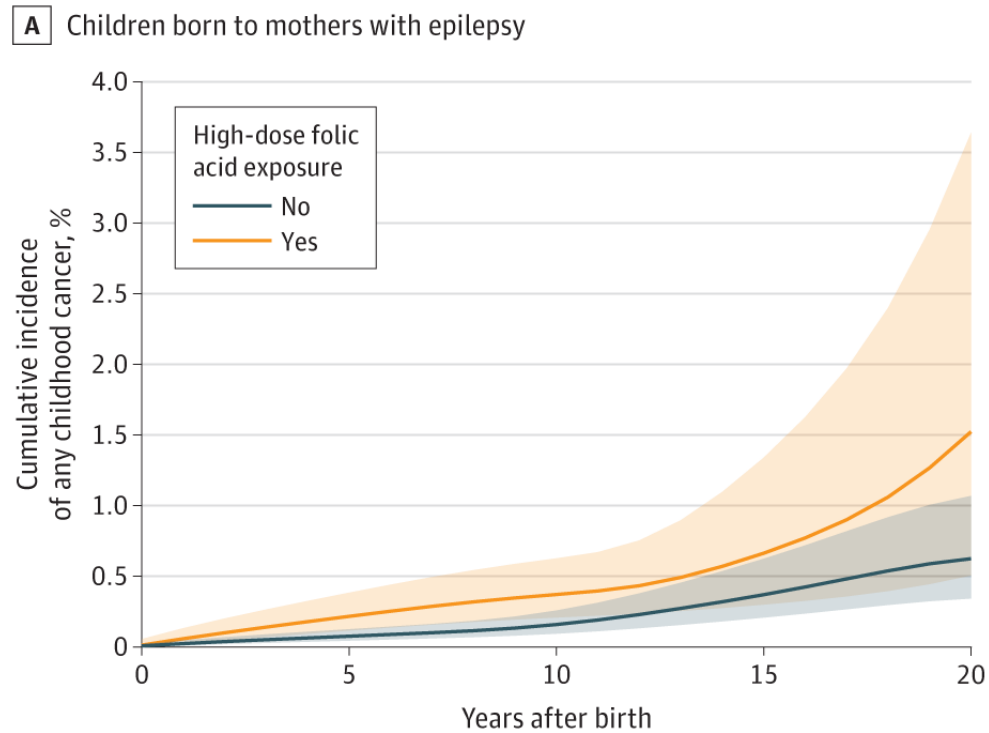
Levetiracetam vs Lamotrigine as First-Line Antiseizure Medication in Female Patients With Idiopathic Generalized Epilepsy

Emanuele Cerulli Irelli, MD, PhD¹; Enrico Cocchi, MD, PhD²; Alessandra Morano, MD, PhD¹; et al

» [Author Affiliations](#)

JAMA Neurol. Published online October 2, 2023. doi:10.1001/jamaneurol.2023.3400

Cancer Risk in Children of Mothers With Epilepsy and High-Dose Folic Acid Use During Pregnancy



High-Dose Folic Acid Use During Pregnancy – Comment und Antwort

- **To the Editor**
- concluded that prenatal exposure to high-dose folic acid is associated with a **2.7-fold increased risk of pediatric cancer**. These findings are based on 18 children with cancer who were born to mothers with epilepsy taking high-dose folic acid (mean dose, 4.3 mg).
- Thus, a **possible interaction** of antiseizure medications with folate or other unaccounted **confounding** factors are probably contributing.
- Our findings indicate that there could be an upper dose limit above which the risks outweigh the benefits. This **suggests an upper limit below the 4 to 5 mg per day recommended dosage to mothers with epilepsy** by some major guidelines (eg, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network).

Genetic Testing to Inform Epilepsy Treatment Management From an International Study of Clinical Practice

- Key Points
- Question How frequently do genetic diagnoses in patients with epilepsy change clinical management, and what are the subsequent patient outcomes?
- Findings In this cross-sectional study among 418 patients with epilepsy who received a genetic diagnosis, 208 (49.8%) had clinical management changes. Of 167 patients with follow-up information, treatment changes were associated with improved patient outcomes in 125 patients (74.9%); the most common improvement was a reduction or elimination of seizures (108 of 167 patients [64.7%]).
- Meaning These findings suggest the use of genetic testing to guide clinical management of patients with epilepsy to improve patient outcomes.

From: **Genetic Testing to Inform Epilepsy Treatment Management From an International Study of Clinical Practice**

JAMA Neurol. 2022;79(12):1267-1276. doi:10.1001/jamaneurol.2022.3651

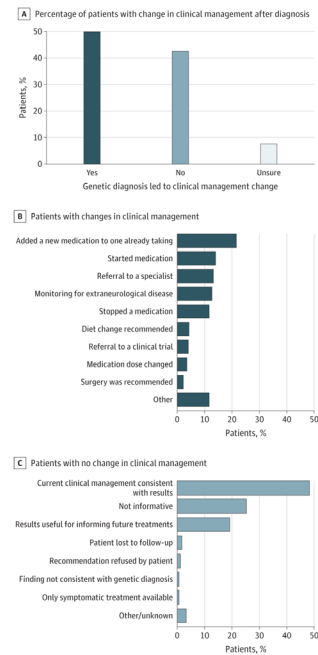


Figure Legend:

Reported Clinical Actions After a Definitive Genetic Diagnosis A, Respondents reported whether the genetic finding influenced a change in clinical management of the patient. B, Those who indicated “yes” selected all of the changes that were implemented or recommended (a patient could have >1 recommendation reported and is counted in each recommendation category). C, Those who indicated “no” reported the reason best describing why no changes were made.

From: Exome Sequencing and the Identification of New Genes and Shared Mechanisms in Polymicrogyria

JAMA Neurol. 2023;80(9):980-988. doi:10.1001/jamaneurol.2023.2363

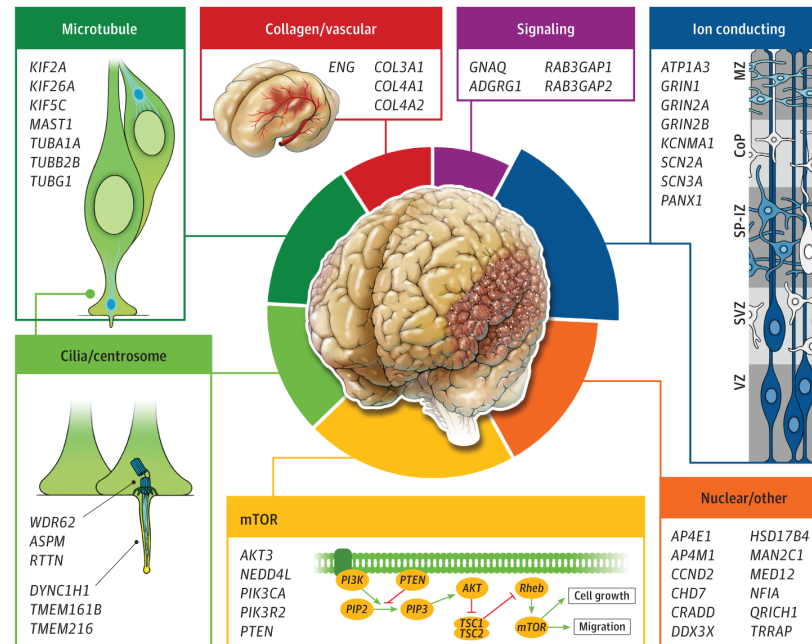


Figure Legend:

Summary of Genes Associated With Polymicrogyria by Category. Relative proportion in each category of polymicrogyria-associated genes identified in this study is summarized. The largest category includes genes encoding mTOR pathway proteins, followed by those encoding ion-conducting proteins. CoP indicates cortical plate; MZ, marginal zone; SP-IZ, subplate intermediate zone; SVZ, subventricular zone; VZ, ventricular zone.