Vogelflug: Neurogenetik

GNP Jahrestagung 2024 in Stuttgart

Prof. Dr. med. Angela Abicht, MGZ-Medizinisch Genetisches Zentrum

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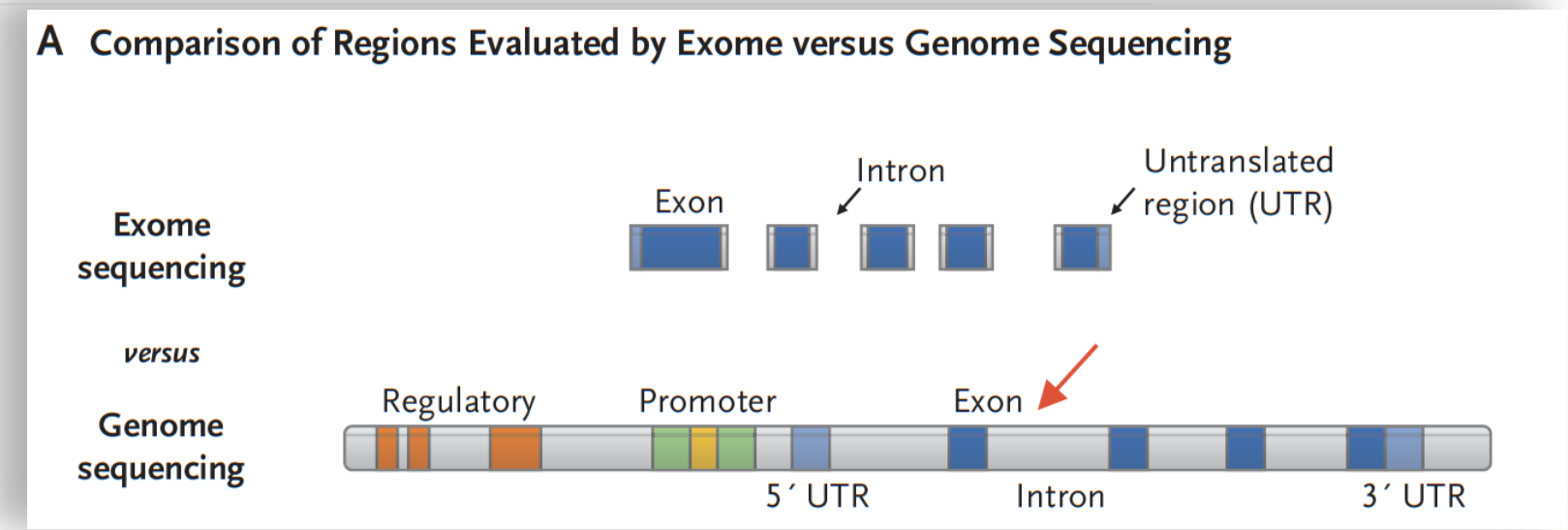
ORIGINAL ARTICLE

Genome Sequencing for Diagnosing Rare Diseases

Authors: Monica H. Wojcik, M.D., M.P.H. , Gabrielle Lemire, M.D., Eva Berger, Maha S. Zaki, M.D., Ph.D., Mariel Wissmann, B.S., Wathone Win, B.S., Susan M. White, M.D., +81 , and Anne O'Donnell-Luria, M.D., Ph.D. Author Info & Affiliations

Published June 5, 2024 | N Engl J Med 2024;390:1985-1997 | DOI: 10.1056/NEJMoa2314761 | VOL. 390 NO. 21



PMID: 38838312

Genome

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Genome Sequencing for Diagnosing Rare Diseases

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Published June 5, 2024 | N Engl J Med 2024;390:1985-1997 | DOI: 10.1056/NEJMoa2314761 | VOL. 390 NO. 21

822 Families

PMID: 38838312

Genome

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Genome Seque

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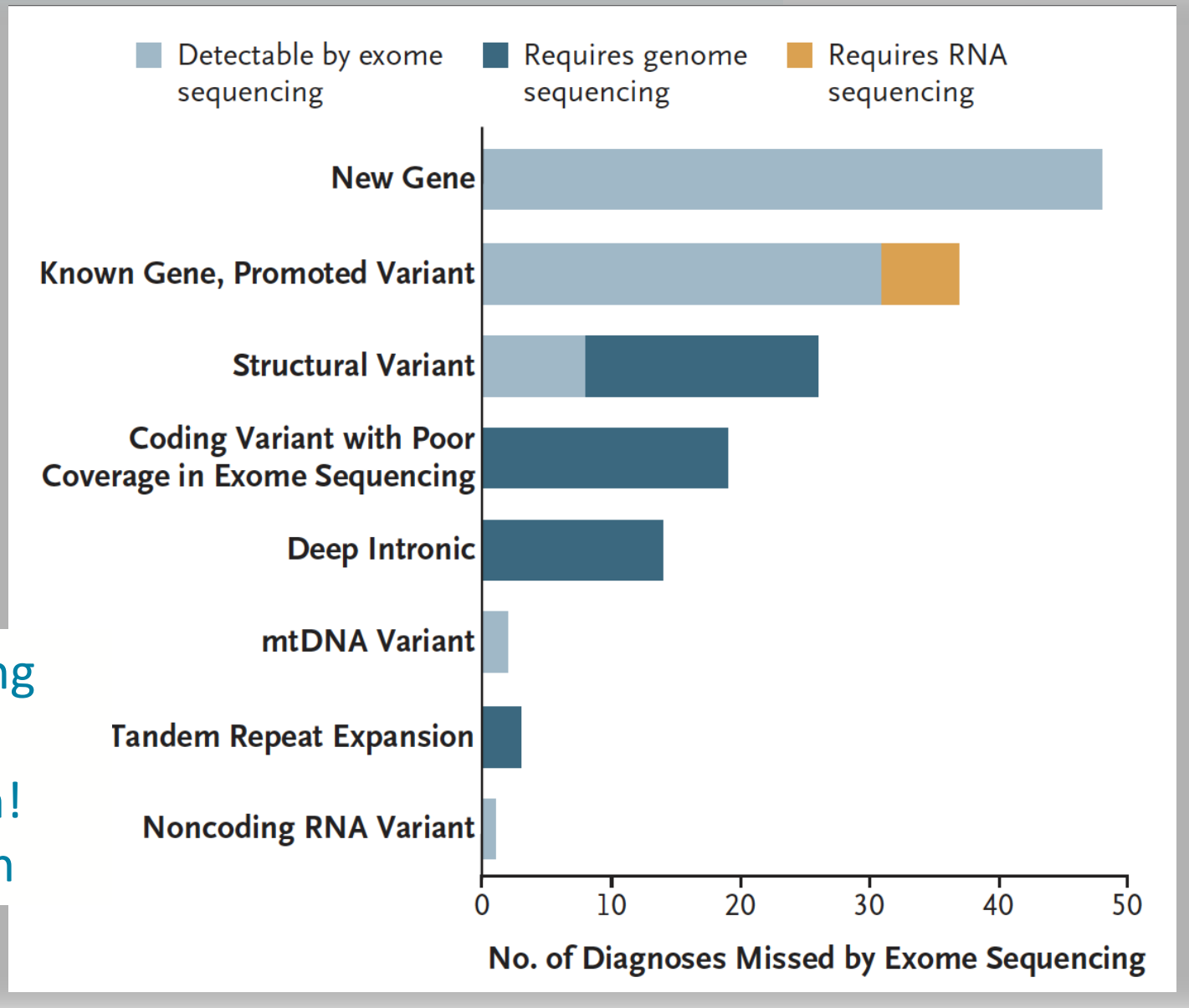

- Technische Verbesserung
- Aktuelle Bioinformatik
- Varianteninterpretation!
- Neue Gene/Phänotypen

PMID: 38838312

Neue Gene?

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RNU4-2

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nature medicine

Brief Communication https://doi.org/10.1038/s41591-024-03085-5

Mutations in the U4 snRNA gene *RNU4-2* cause one of the most prevalent monogenic neurodevelopmental disorders

Received: 11 April 2024
Accepted: 23 May 2024
Published online: 31 May 2024
Check for updates

Daniel Greene[1,2], Chantal Thys[3], Ian R. Berry[4,5], Joanna Jarvis[6], Els Ortibus[7,8], Andrew D. Mumford[5,9], Kathleen Freson[3] & Ernest Turro[1,2,10,11]

Most people with intellectual disability (ID) do not receive a molecular diagnosis following genetic testing. To identify new etiologies of ID, we performed a genetic association analysis comparing the burden of rare ...es and ...lear

- 47 Patienten

Greene D, et al. Nat Med. 2024 Aug;30:2165-2169.
PMID: 38821540

Article

De novo variants in the *RNU4-2* snRNA cause a frequent neurodevelopmental syndrome

https://doi.org/10.1038/s41586-024-07773-7
Received: 7 April 2024
Accepted: 2 July 2024
Published online: 11 July 2024
Open access
Check for updates

Around 60% of individuals with neurodevelopmental disorders (NDD) remain undiagnosed after comprehensive genetic testing, primarily of protein-coding genes[1]. Large genome-sequenced cohorts are improving our ability to discover new diagnoses in the non-coding genome. Here we identify the non-coding RNA *RNU4-2* as a syndromic NDD gene. *RNU4-2* encodes the U4 small nuclear RNA (snRNA), which is a critical component of the U4/U6.U5 tri-snRNP complex of the major spliceosome[2]. We identify an 18 base pair region of *RNU4-2* mapping to two structural elements in the U4/U6 snRNA duplex (the T-loop and stem III) that is severely depleted of variation in the general population, but in which we identify heterozygous variants in 115 individuals with NDD. Most individuals (77.4%) have the same highly recurrent single base insertion (n.64_65insT). In 54 individuals in whom it could be determined, the de novo variants were all on the maternal allele. We demonstrate that *RNU4-2* is highly expressed in the developing human brain, in contrast to *RNU4-1* and other U4 ...is systematically ...own role of this ...nts in this 18 base pair region explain 0.4% of individuals with NDD. This work underscores the importance of non-coding genes in rare disorders and will provide a diagnosis to thousands of individuals with NDD worldwide.

- 115 Patienten

Chen Y, et al. Nature. 2024 Aug;632:832-840.
PMID: 38991538

RNU4-2

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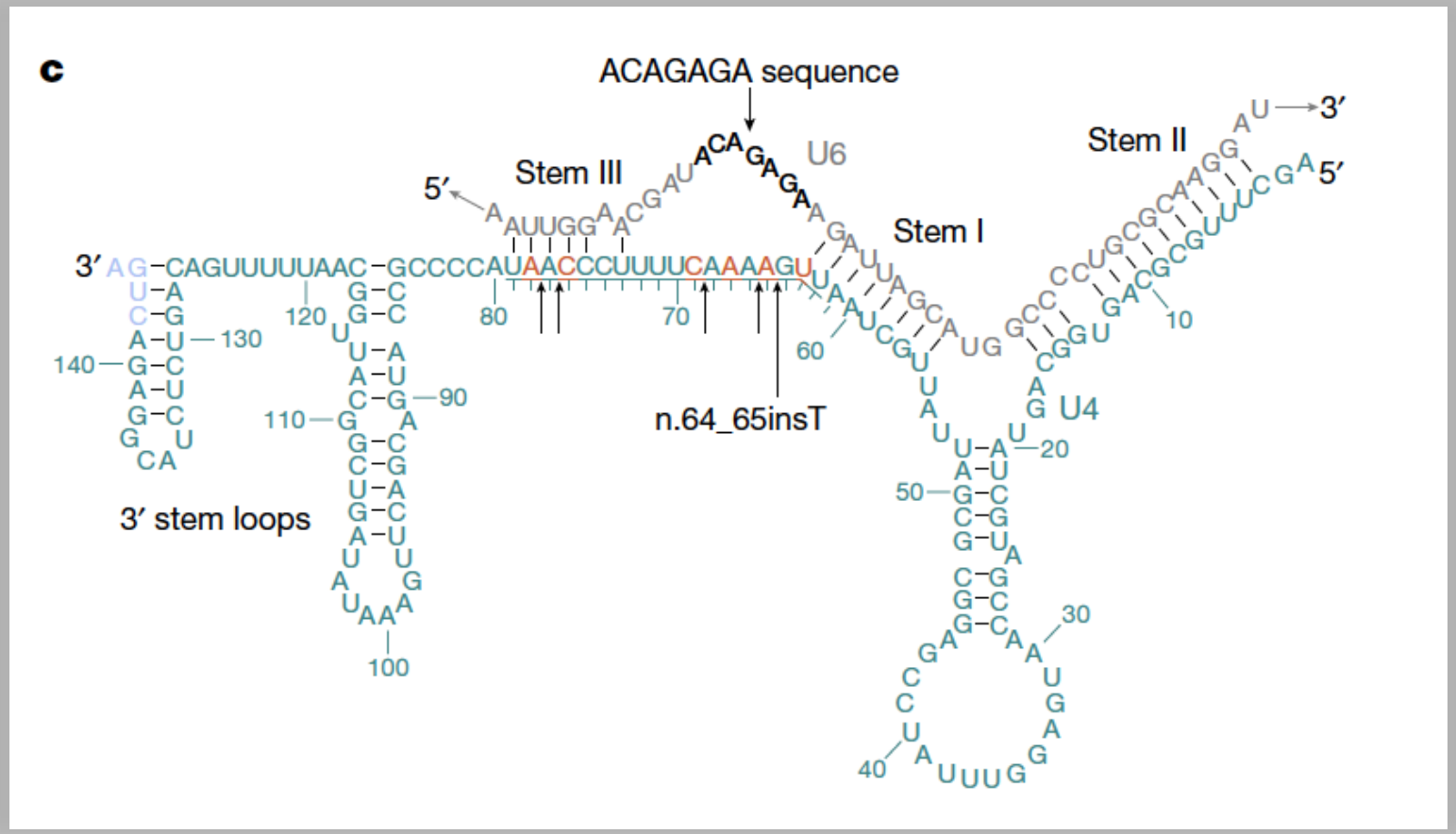

- Monoallelische de de novo Varianten in einer konservierten 18bp Region
- 1 hochrekurrente single base insertion (n.64_65insT) (77% der Patienten)

Chen Y, et al. Nature. 2024 Aug;632:832-840.
PMID: 38991538

RNU4-2

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- Moderat bis schwere globale Entwicklungsverzögerung, geistige Behinderung
- Meiste Patienten non-verbal
- Faziale Dysmorphien (myopathische Fazies, große tief angesetzte Ohren, typische Mundpartie)
- Variabel: Hypotonie, Kleinwuchs, Mikrocephalie, Epilepsie, unterschiedliche Befunde im cMRT, Sehstörungen, hormonelle Auffälligkeiten, Fehlbildungen

Chen Y, et al. Nature. 2024 Aug;632:832-840.
PMID: 38991538

- Could explain 0.4% of all NDD

Methylation Signatures

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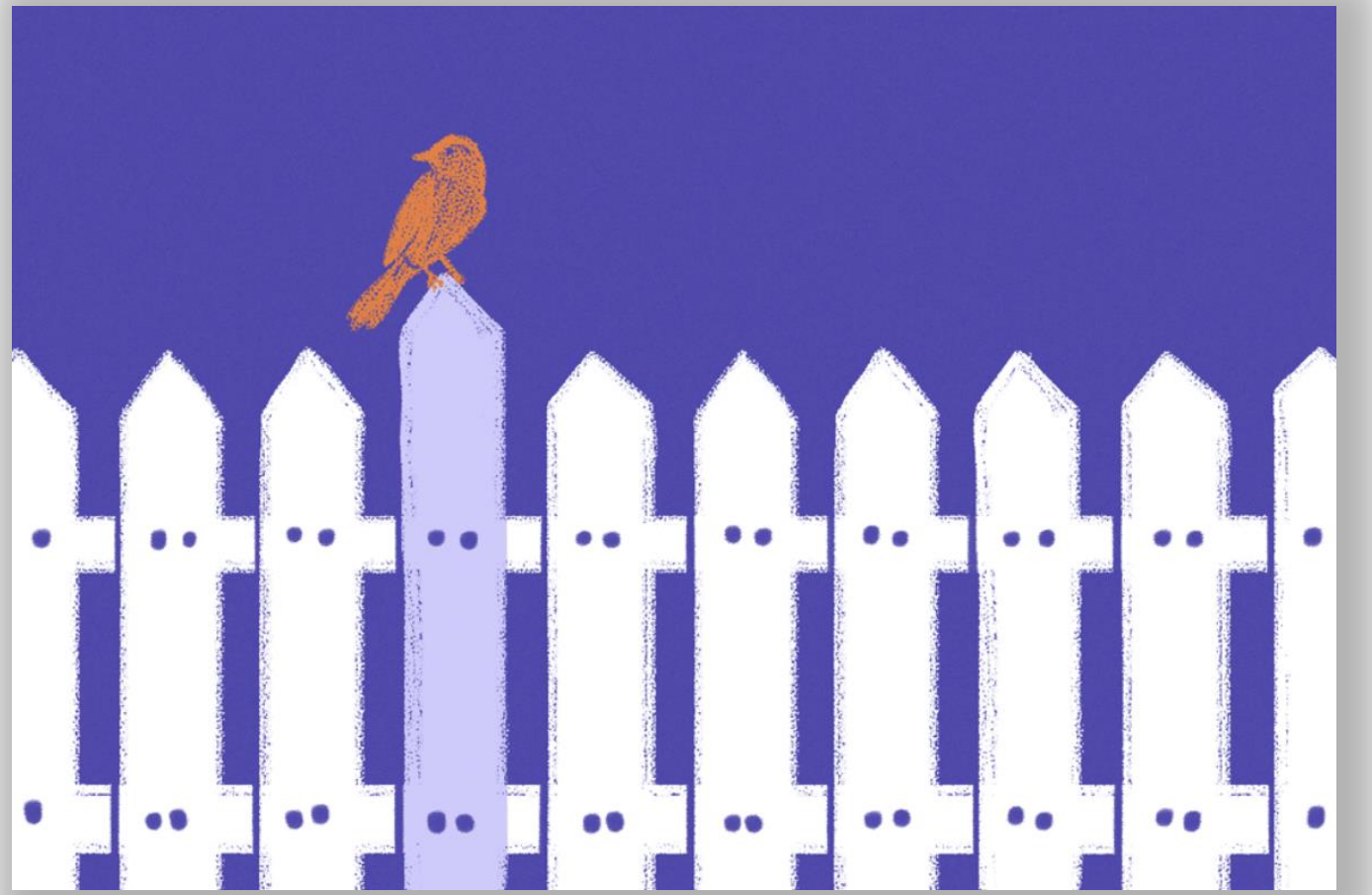

https://www.excedr.com/resources/what-is-dna-methylation

Methylation Signatures

The detection of a strong **episignature** for Chung-Jansen syndrome, partially overlapping with Borjeson-Forssman-Lehmann and White-Kernohan syndromes.

Vos N, Haghshenas S, van der Laan L, Russel PKM, Rooney K, Levy MA, Relator R, Kerkhof J, McConkey H, Maas SM, Vissers LELM, de Vries BBA, Pfundt R, Elting MW, van Hagen JM, Verbeek NE, Jongmans MCJ, Lakeman P, Rumping L, Bosch DGM, Vitobello A, Thauvin-Robinet C, Faivre L, Nambot S, Garde A, Willems M, Genevieve D, Nicolas G, Busa T, Toutain A, Gérard M, Bizaoui V, Isidor B, Merla G, Accadia M, Schwartz CE, Ounap K, Hoffer MJV, Nezarati MM, van den Boogaard MH, Tedder ML, Rogers C, Brusco A, Ferrero GB, Spodenkiewicz M, Sidlow R, Mussa A, Trajkova S, McCann E, Mroczkowski HJ, Jansen S, Donker-Kaat L, Duijkers FAM, Stuurman KE, Mannens MMAM, Alders M, Henneman P, White SM, Sadikovic B, van Haelst MM.

Hum Genet. 2024 Jun;143(6):761-773. doi: 10.1007/s00439-024-02679-w. Epub 2024 May 24.

PMID: 38787418 **Free PMC article.**

> Genet Med. 2024 Sep 28:101283. doi: 10.1016/j.gim.2024.101283. Online ahead of print.

Microduplications of ARID1A and ARID1B cause a novel clinical and epigenetic distinct BAFopathy

Pleuntje J van der Sluijs [1], Sébastien Moutton [2], Alexander J M Dingemans [3], Denisa Weis [4], Michael A Levy [5], Kym M Boycott [6], Claudia Arberas [7], Margherita Baldassarri [8], Claire Beneteau [9], Alfredo Brusco [10], Charles Coutton [11], Tabib Dabir [12], Maria L Dentici [13], Koenraad Devriendt [14], Laurence Faivr, Marlies J Kempers [3], Jennifer Kerkhof, Nathalie Marle [20], Haley McConkey [21], Marcello Niceta [24], Claire Nicolas [15], A, Julia Rankin [27], Raissa Relator [5], Fabie, Sarah A Sandaradura [31], Elena Shukarc, Marco Tartaglia [34], Matthew A Tedder, Jeremy Woods [38], Bert B A de Vries [3]

Affiliations + expand

PMID: 39355979 DOI: 10.1016/j.gim.2024.101283

Diagnosis of TET3-Related Beck-Fahrner Syndrome in an Individual With Chorioretinal and Iris Colobomata Using a DNA Methylation Signature.

Man A, Di Scipio M, McConkey H, Hough R, Stein N, Diehl E, Marshall CR, Sadikovic B, Ejaz R.

Am J Med Genet A. 2024 Sep 26:e63864. doi: 10.1002/ajmg.a.63864. Online ahead of print.

PMID: 39324309

Discovery of DNA methylation signature in the peripheral blood of in with history of antenatal exposure to valproic acid.

Haghshenas S, Putoux A, Reilly J, Levy MA, Relator R, Ghosh S, Kerkhof J, McConkey Lesca G, Besson A, Coubes C, Willems M, Ruiz-Pallares N, Barat-Houari M, Tizzano E Sabbagh Q, Clayton-Smith J, Jackson A, O'Sullivan J, Bromley R, Banka S, Genevieve

Genet Med. 2024 Oct;26(10):101226. doi: 10.1016/j.gim.2024.101226. Epub 2024 Jul

PMID: 39097820

> Am J Hum Genet. 2024 Aug 8;111(8):1643-1655. doi: 10.1016/j.ajhg.2024.07.005. Epub 2024 Jul 31.

Identification of a DNA methylation episignature for recurrent constellations of embryonic malformations

Sadegheh Haghshenas [1], Karim Karimi [1], Roger E Stevenson [2], Michael A Levy [1], Raissa Relator [1], Jennifer Kerkhof [1], Jessica Rzasa [1], Haley McConkey [3], Carolyn Lauzon-Young [3], Tugce B Balci [4], Alexandre M White-Brown [5], Melissa T Carter [6], Julie Richer [6], Christine M Armour [6], Sarah L Sawyer [6], Priya T Bhola [6], Matthew L Tedder [2], Cindy D Skinner [2], Iris A L M van Rooij [7], Romy van de Putte [7], Ivo de Blaauw [8], Rebekka M Koeck [9], Alexander Hoischen [10], Han Brunner [11], Masoud Zamani Esteki [9], Anna Pelet [12], Stanislas Lyonnet [13], Jeanne Amiel [13], Kym M Boycott [14], Bekim Sadikovic [15]

Affiliations + expand

PMID: 39089258 PMCID: PMC11339616 (available on 2025-02-08)

Methylation Signatures

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Article | Open access | Published: 06 August 2024

Diagnostic utility of DNA methylation analysis in genetically unsolved pediatric epilepsies and CHD2 episignature refinement

Christy W. LaFlamme, Cassandra Rastin, Soham Sengupta, Helen E. Pennington, Sophie J. Russ-Hall, Amy L. Schneider, Emily S. Bonkowski, Edith P. Almanza Fuerte, Talia J. Allan, Miranda Perez-Galey Zalusky, Joy Goffena, Sophia B. Gibson, Denis M. Nyaga, Nico Lieffering, Malavika Hebbar, Emily V. Walker, Daniel Darnell, Scott R. Olsen, Pandurang Kolekar, Mohamed Nadhir Djekidel, Wojciech Rosikiewicz, Haley McConkey, Jennifer Kerkhof, Michael A. Levy, Undiagnosed Diseases Network, University of Washington Center for Rare Disease Research, ... Heather C. Mefford

+ Show authors

Nature Communications **15**, Article number: 6524 (2024) | Cite this article

PMID: 39107278

582 individuals with genetically unsolved DEEs

12 solved cases by the identification of DMRs or episignatures

Strukturvarianten

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Strukturvarianten

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+ by improved bioinformatics

ARTICLE OPEN

Check for updates

Structural variant calling and clinical interpretation in 6224 unsolved rare disease exomes

German Demidov[1✉], Steven Laurie[2], Annalaura Torella[3,4], Giulio Piluso[3], Marcello Scala[5,6], Manuela Morleo[3,4], Vincenzo Nigro[3,4], Holm Graessner[1,7], Siddharth Banka[8,9], Solve-RD consortium*, Katja Lohmann[10] and Stephan Ossowski[1]

Structural variants (SVs), including large deletions, duplications, inversions, translocations, and more complex events have the potential to disrupt gene function resulting in rare disease. Nevertheless, current pipelines and clinical decision support systems for exome sequencing (ES) tend to focus on small alterations such as single nucleotide variants (SNVs) and insertions-deletions shorter than 50 base pairs (indels). Additionally, detection and interpretation of large copy-number variants (CNVs) are frequently performed. However, detection of other types of SVs in ES data is hampered by the difficulty of identifying breakpoints in off-target (intergenic or intronic) regions, which makes robust identification of SVs challenging. In this paper, we demonstrate the utility of SV calling in ES resulting in a diagnostic yield of 0.4% (23 out of 5825 probands) for a large cohort of unsolved patients collected by the Solve-RD consortium. Remarkably, 8 out of 23 pathogenic SV were not found by comprehensive read-depth-based CNV analysis, resulting in a 0.13% increased diagnostic value.

European Journal of Human Genetics (2024) 32:998–1004; https://doi.org/10.1038/s41431-024-01637-4

PMID: 38822122

Strukturvarianten

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Research Article

TRANSPARENT PROCESS SOURCE DATA OPEN ACCESS

Life Science Alliance

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Biallelic structural variations within *FGF12* detected by long-read sequencing in epilepsy

Sachiko Ohori[1,2], Akihiko Miyauchi[3], Hitoshi Osaka[3], Charles Marques Lourenco[4,5], Naohiro Arakaki[6,7], Toru Sengoku[8], Kazuhiro Ogata[8], Rachel Sayuri Honjo[9], Chong Ae Kim[9], Satomi Mitsuhashi[10], Martin C Frith[11,12,13], Rie Seyama[1,14], Naomi Tsuchida[1,15], Yuri Uchiyama[1,15], Eriko Koshimizu[1], Kohei Hamanaka[1], Kazuharu Misawa[1], Satoko Miyatake[1,16], Takeshi Mizuguchi[1], Kuniaki Saito[6,7], Atsushi Fujita[1], Naomichi Matsumoto[1]

PMID: 37286232

Strukturvarianten

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Research Article

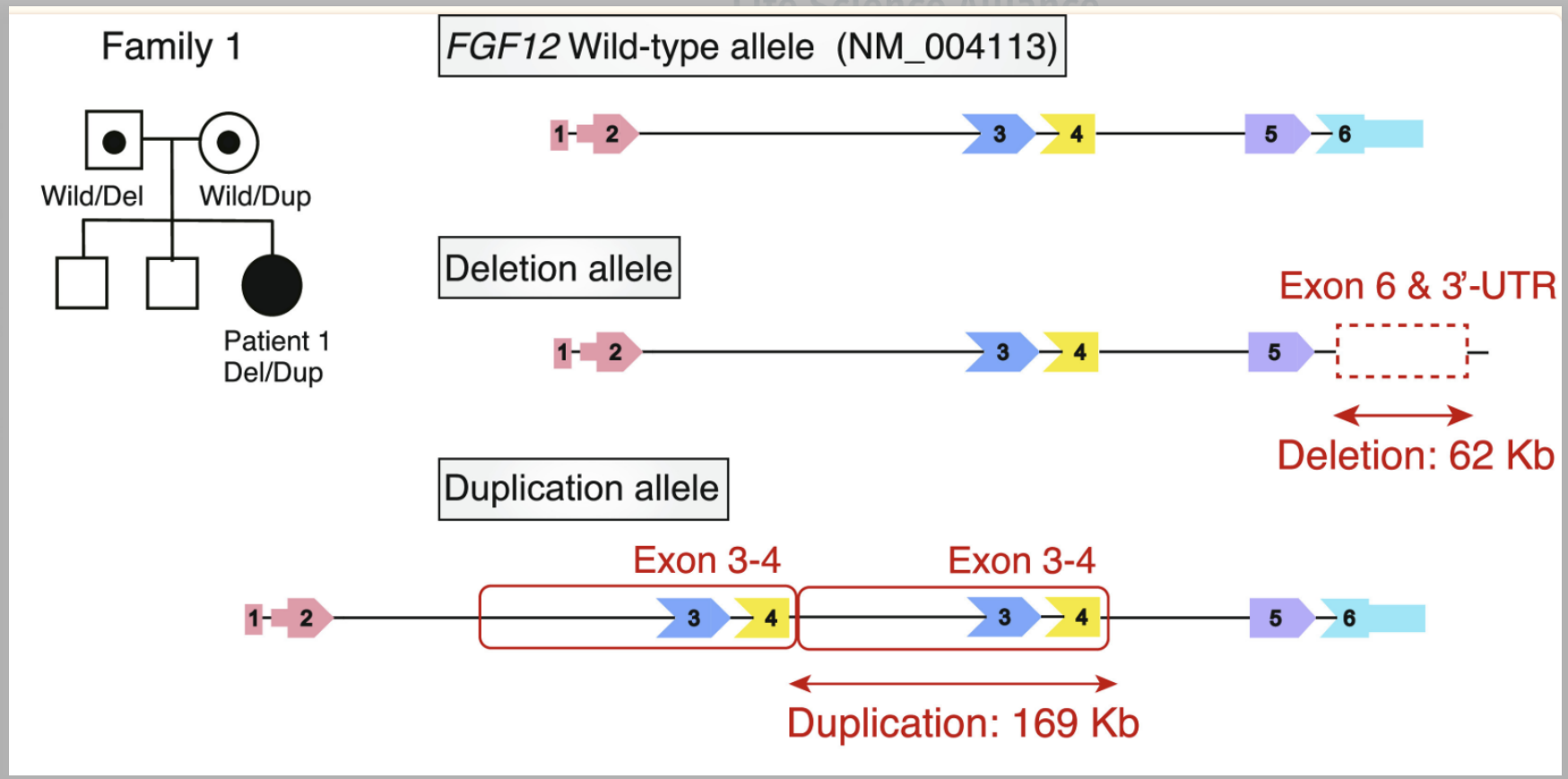
TRANSPARENT PROCESS SOURCE DATA OPEN ACCESS

Life Science Alliance

Check for updates

Biallelic structu
long-read seque

Sachiko Ohori[1,2], Akihiko Miyau
Toru Sengoku[8], Kazuhiro Ogata
Rie Seyama[1,14], Naomi Tsuchid
Satoko Miyatake[1,16], Takeshi Mizu



PMID: 37286232

Digenic Inheritance

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Digenic Inheritance

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nature > nature genetics > articles > article

Article | Open access | Published: 01 March 2024

Digenic inheritance involving a muscle-specific protein kinase and the giant titin protein causes a skeletal muscle myopathy

Ana Töpf, Dan Cox, Irina T. Zaharieva, Valeria Di Leo, Jaakko Sarparanta, Per Harald Jonson, Ian M. Sealy, Andrei Smolnikov, Richard J. White, Anna Vihola, Marco Savarese, Munise Merteroglu, Neha Wali, Kristen M. Laricchia, Cristina Venturini, Bas Vroling, Sarah L. Stenton, Beryl B. Cummings, Elizabeth Harris, Chiara Marini-Bettolo, Jordi Diaz-Manera, Matt Henderson, Rita Barresi, Jennifer Duff, ... Volker Straub + Show authors

Nature Genetics **56**, 395–407 (2024) | Cite this article

PMID: 38429495

Digenic Inheritance

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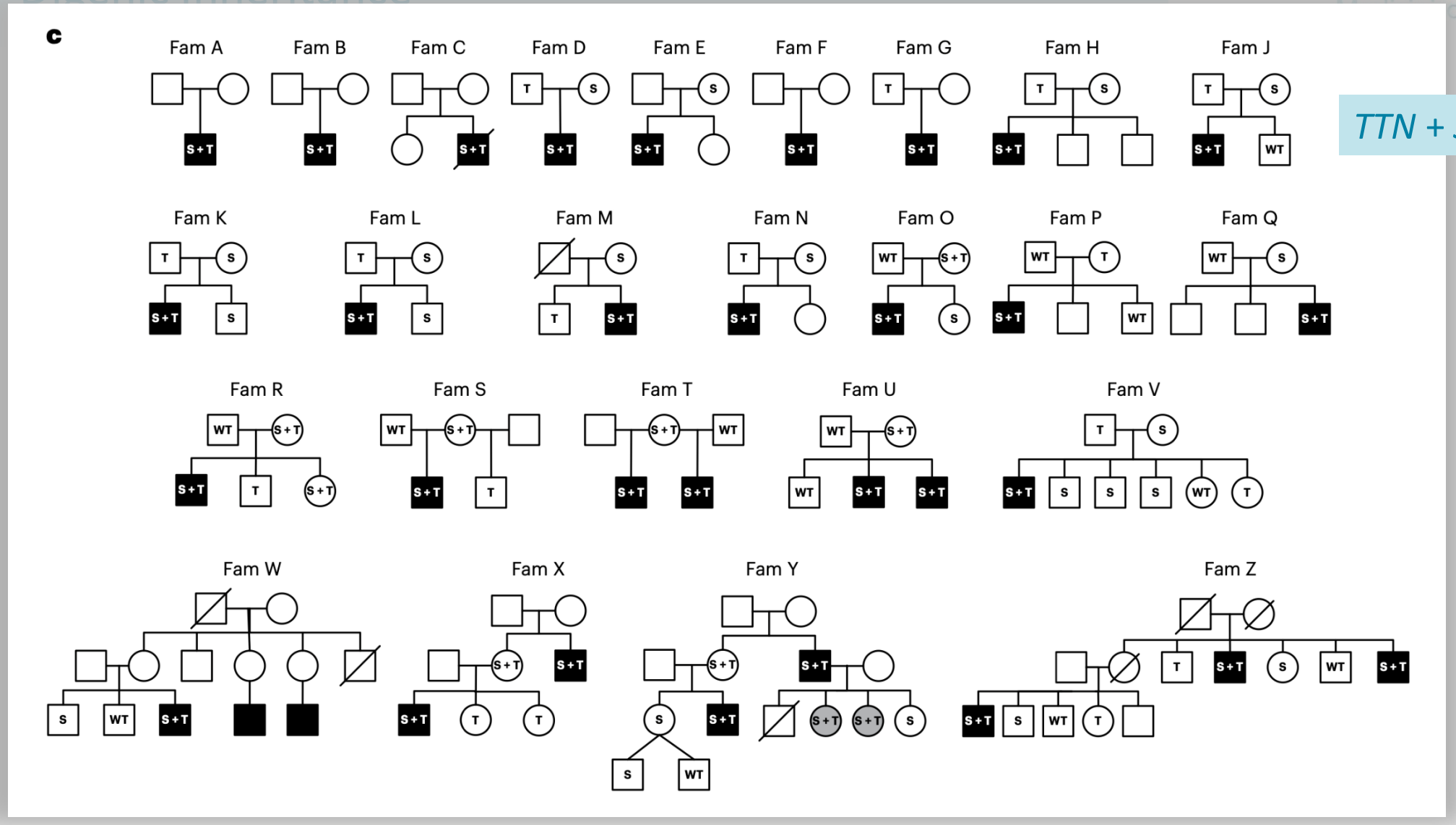

TTN + SRPK3

PMID: 38429495

Mosaike

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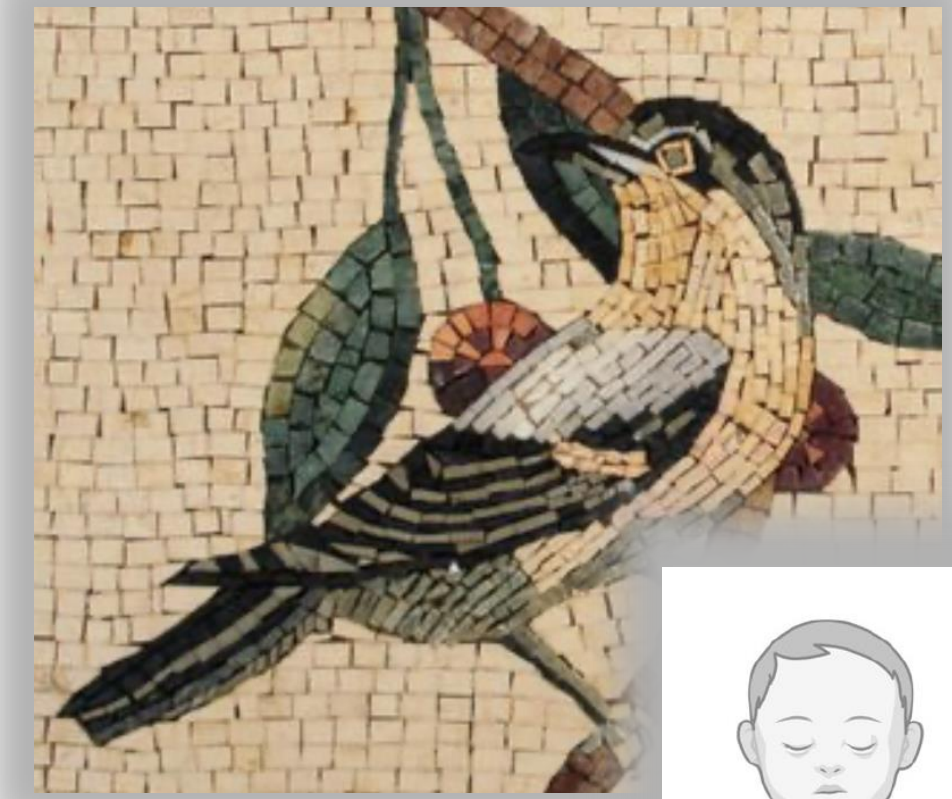
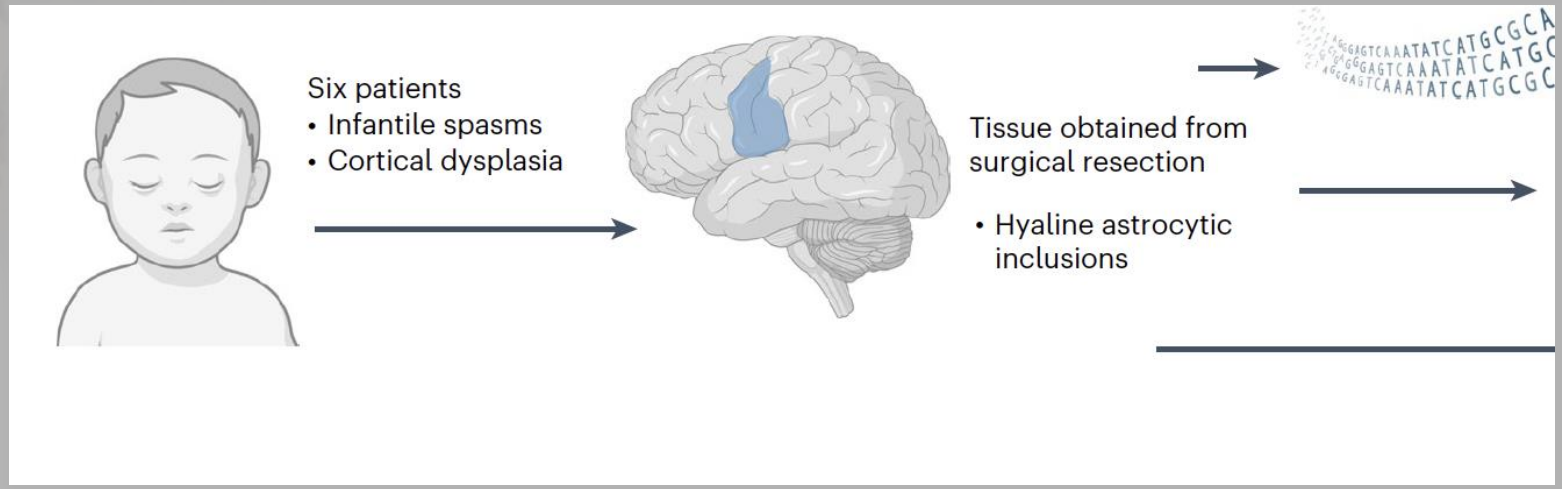


https://www.mosaicnatural.de/mosaics/mosaik-vogel-an121



PMID: 37872450

Mosaic alterations

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› Brain. 2024 Sep 3;147(9):2983-2990. doi: 10.1093/brain/awae190.

Threshold of somatic mosaicism leading to brain dysfunction with focal epilepsy

Jintae Kim [1], Sang Min Park [1 2], Hyun Yong Koh [3], Ara Ko [1 4], Hoon-Chul Kang [5], Won Seok Chang [5], Dong Seok Kim [5], Jeong Ho Lee [1 2]

PMID: 38916065

Mosaic alterations

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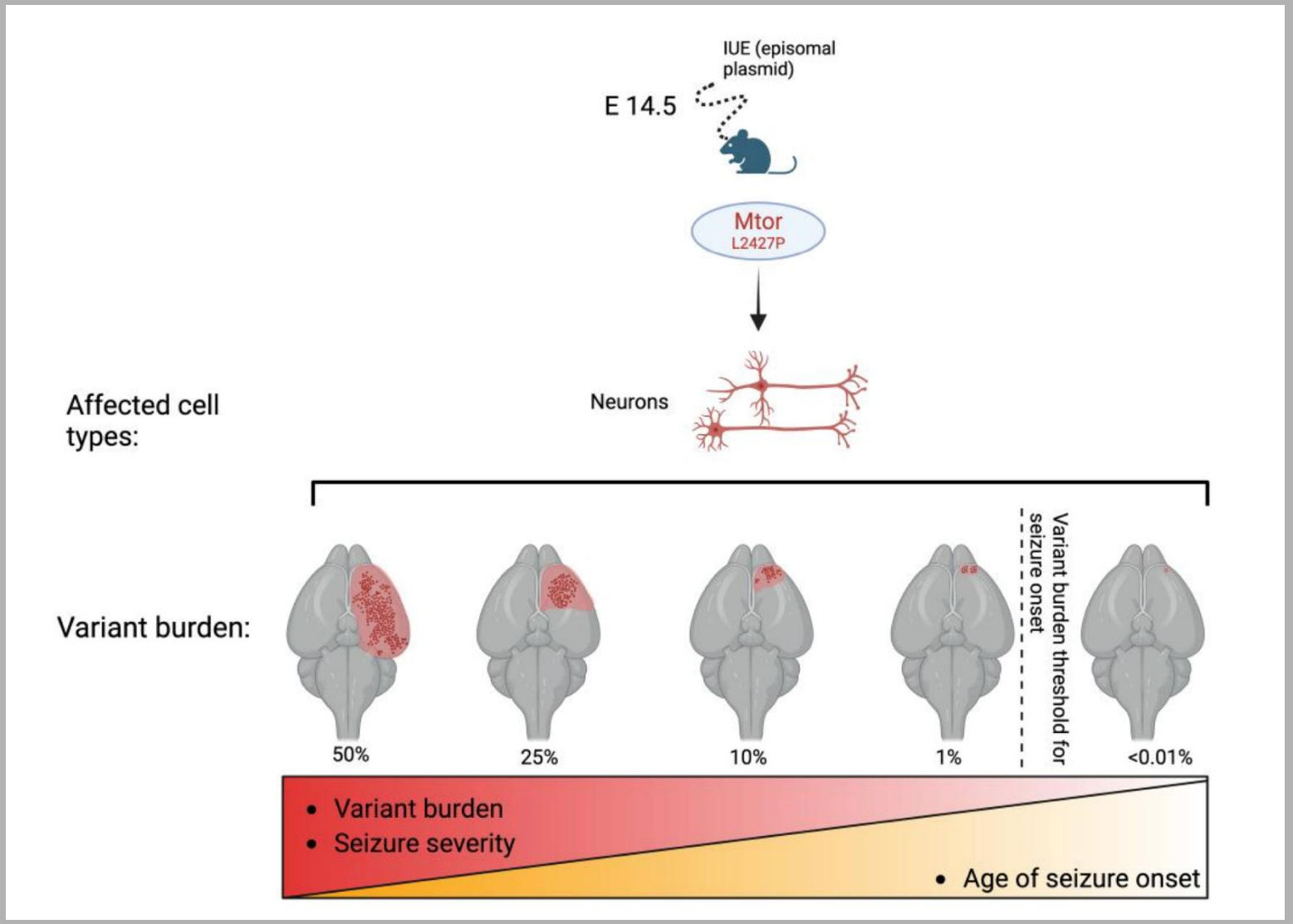
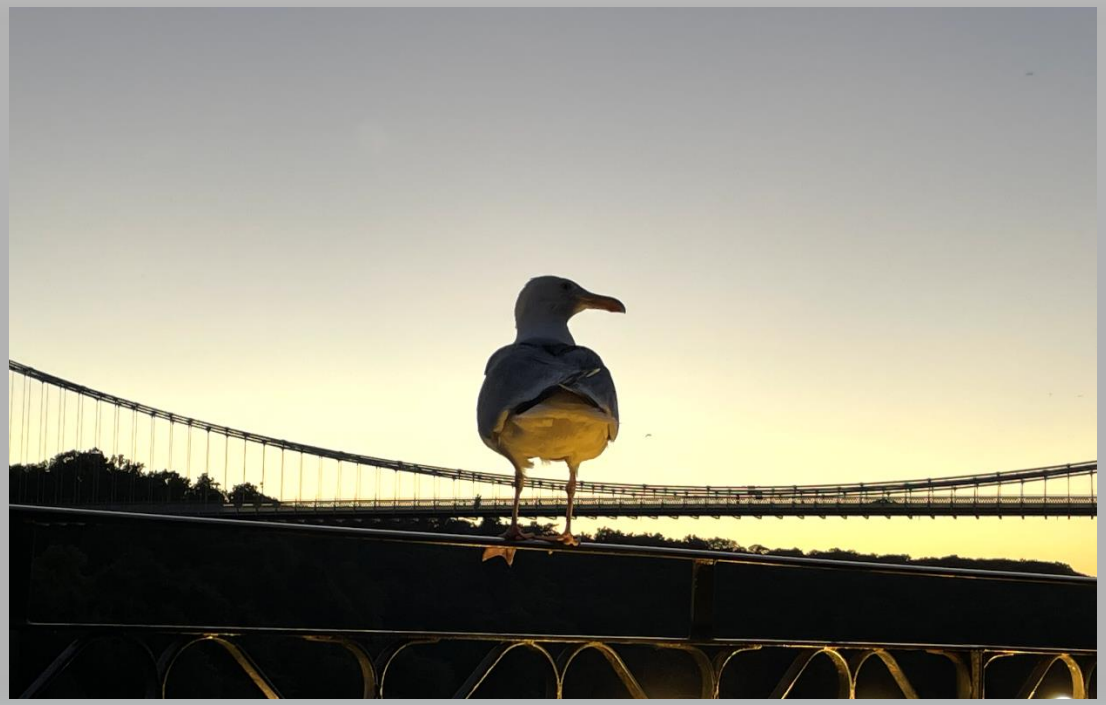
› Brain. 2024 Sep 3;147(9):2983-2

Threshold of somat
dysfunction with fo

Jintae Kim [1], Sang Min Park [1 2], Hy
Won Seok Chang [5], Dong Seok Kim



PMID: 38916065



VIELEN DANK FÜR
IHRE AUFMERKSAMKEIT

Digenic Inheritance

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Brain. 2024 Jun; 147(6): 1967–1974.
Published online 2024 Mar 13. doi: 10.1093/brain/awae057

PMCID: PMC11146415
PMID: 38478578

Digenic Leigh syndrome on the background of the m.11778G>A Leber hereditary optic neuropathy variant

Beryll Blickhäuser, Sarah L Stenton, Christiane M Neuhofer, Elisa Floride, Victoria Nesbitt, Carl Fratter, Johannes Koch, Birgit Kauffmann, Claudia Catarino, Lea Dewi Schlieben, Robert Kopajtich, Valerio Carelli, Alfredo A Sadun, Robert McFarland, Fang Fang, Chiara La Morgia, Stéphanie Paquay, Marie Cécile Nassogne, Daniele Ghezzi, Costanza Lamperti, Saskia Wortmann, Jo Poulton, Thomas Klopstock, and Holger Prokisch