List of SCN2A articles

October 2020	Neonatal SCN2A encephalopathy: A peculiar recognizable electroclinical sequence *Gia Melikishvili, Olivier Dulac, Svetlana Gataullina* Sodium voltage-gated channel alpha subunit 2 (SCN2A) gene encodes the Nav1.2 subunit of voltage-gated sodium channel in pyramidal neurons. SCN2A gain-of-function mutations are identified more and more often with gene panels and whole exome sequencing. Phenotype ranges from benign neonatal or infantile seizures to severe epileptic encephalopathy. Although large series of patients targeting genetic background point out two main phenotypes with SCN2A encephalopathy, Ohtahara syndrome and malignant migrating partial seizures in infancy (EMPSI), we noticed that in fact, a peculiar clinical and electroencephalogram (EEG) sequence distinct from these syndromes should suggest the diagnosis early...
October 2020	Diagnostic gap in genetic epilepsies: A matter of age *Angel Aledo-Serrano, Irene García-Morales, Rafael Toledano, Adolfo Jiménez-Huete, Beatriz Parejo, Carla Anciones, Ana Mingorance, Primitivo Ramos, Antonio Gil-Nagel* Objective - This study aimed to evaluate the access to advanced diagnostic tests in patients with epilepsy and intellectual disability, with special focus on genetics. Methods - Patients with epilepsy and intellectual disability evaluated between 2016 and 2018 at the Epilepsy Unit of two hospitals in Madrid, Spain were included. The main inclusion criterion was an undetermined etiological diagnosis after clinical assessment, neuroimaging, and electroencephalogram (EEG). Results - Two hundred and five patients with epilepsy and intellectual disability were evaluated, with 124 fulfilling the inclusion criteria (mean age: 33.9 years). Regarding the etiological workup, advanced neuroimaging, prolonged video-EEG, and any type of genetic test had been performed in 58%, 41%, and 40%, respectively. An etiological diagnosis was reached in 18.5%. The workup was considered incomplete in 67%...
August 2020	Parabens inhibit hNaV 1.2 channels *Andrea Enrique, Pedro Martín, María Laura Sbaraglini, Alan Talevi, Verónica Milesi* Propylparaben, a commonly used antimicrobial preservative, has been reported as an anticonvulsant agent targeting neuronal Na+ channels (NaV). However, the specific features of the NaV channel inhibition by this agent have so far not been extensively studied. Moreover, it is still unclear if it shares this pharmacological activity with other parabens. Here, we fully characterized the mechanism of action of the inhibitory effect that propylparaben and benzylparaben induce on human NaV 1.2 channel isoform (hNaV1.2)…

July 2020	[Overrepresentation of genetic variation in the AnkyrinG interactome is related to a range of neurodevelopmental disorders] *Ilse M. van der Werf, Sandra Jansen, Petra F. de Vries, Amber Gerstmans, Maartje van de Vorst, Anke Van Dijck, Bert B. A. de Vries, Christian Gilissen, Alexander Hoischen, Lisenka E. L. M. Vissers, R. Frank Kooy, Geert Vandeweyer* Upon the discovery of numerous genes involved in the pathogenesis of neurodevelopmental disorders, several studies showed that a significant proportion of these genes converge on common pathways and protein networks. Here, we used a reversed approach, by screening the AnkyrinG protein-protein interaction network for genetic variation in a large cohort of 1009 cases with neurodevelopmental disorders. We identified a significant enrichment of de novo potentially disease-causing variants in this network, confirming that this protein network plays an important role in the emergence of several neurodevelopmental disorders...
July 2020	[Genetic diagnosis and clinical characteristics by etiological classification in early-onset epileptic encephalopathy with burst suppression pattern] *Sangbo Lee, Se Hee Kim, Borahm Kim, Seung-Tae Lee, Jong Rak Choi, Heung Dong Kim, Joon Soo Lee, Hoon-Chul Kang* Early-onset epileptic encephalopathies with burst suppression (EOEE-BS) are a group of neonatal epileptic syndromes characterized by intractable epilepsy and severe psychomotor delay with structural and metabolic factors accounting for major etiologies. However, recent advances in gene sequencing have identified that genetic factors might also play a significant role in the development of EOEE-BS. Herein, we used various genetic tests to identify pathogenic genetic variants in EOEE-BS irrespective of structural malformations and analyzed the clinical features associated with each different etiology...

June 2020	[Isoform transcriptome of developing human brain provides new insights into autism risk variants] *Kevin Chau, Pan Zhang, Jorge Urresti, Megha Amar, Akula Bala Pramod, Amy Thomas, Roser Corominas, Guan Ning Lin, Lilia M. Iakoucheva* Alternative splicing plays important role in brain development, however its global contribution to human neurodevelopmental diseases (NDD) has not been fully investigated. Here, we examined the relationships between splicing isoforms expression in the brain and de novo loss-of-function mutations identified in the patients with NDDs. We constructed isoform transcriptome of the developing human brain, and observed differentially expressed isoforms and isoform co-expression modules undetectable by the gene-level analyses. These isoforms were enriched in loss-of-function mutations and microexons, co-expressed with a unique set of partners, and had higher prenatal expression. We experimentally tested the impact of splice site mutations in five NDD risk genes, including SCN2A, DYRK1A and BTRC, and demonstrated exon skipping. Furthermore, our results suggest that the splice site mutation in BTRC reduces translational efficiency, likely impacting Wnt signaling through impaired degradation of β-catenin. We propose that functional effect of mutations associated with human diseases should be investigated at isoform- rather than gene-level resolution...
June 2020	[Characterization of a gene-trap knockout mouse model of SCN2A encoding voltage-gated sodium channel NaV1.2] *Muriel Eaton, Jingliang Zhang, Zhixiong Ma, Anthony C. Park, Emma Lietzke, Chloé Maricela Romero, Yushuang Liu, Emily Rose Coleman, Xiaoling Chen1,2, Tiange Xiao, Zhuo Huang, William C. Skarnes, Wendy A. Koss, Yang Yang* Recent large-scale genomic studies have revealed SCN2A as one of the most frequently mutated gene in patients with neurodevelopmental disorders including autism spectrum disorder and intellectual disability. SCN2A encodes for voltage-gated sodium channel isoform 1.2 (NaV1.2), which is mainly expressed in the central nervous system and responsible for the propagation of neuronal action potentials. Homozygous knockout (null) of SCN2A is perinatal lethal, whereas heterozygous knockout of SCN2A results in mild behavior abnormalities...

June 2020	[mTADA is a framework for identifying risk genes from de novo mutations in multiple traits] *Tan-Hoang Nguyen, Amanda Dobbyn, Ruth C. Brown, Brien P. Riley, Joseph D. Buxbaum, Dalila Pinto, Shaun M. Purcell, Patrick F. Sullivan, Xin He, Eli A. Stahl* Joint analysis of multiple traits can result in the identification of associations not found through the analysis of each trait in isolation. Studies of neuropsychiatric disorders and congenital heart disease (CHD) which use de novo mutations (DNMs) from parent-offspring trios have reported multiple putatively causal genes. However, a joint analysis method designed to integrate DNMs from multiple studies has yet to be implemented. We here introduce multiple-trait TADA (mTADA) which jointly analyzes two traits using DNMs from non-overlapping family samples...
Mai 2020	[Ion channels involvement in neurodevelopmental disorders] *Maria Cristina D'Adamo, Antonella Liantonio, Elena Conte, Mauro Pessia, Paola Imbrici* Inherited and sporadic mutations in genes encoding for brain ion channels, affecting membrane expression or biophysical properties, have been associated with neurodevelopmental disorders characterized by epilepsy, cognitive and behavioral deficits with significant phenotypic and genetic heterogeneity. Over the years, the screening of a growing number of patients and the functional characterization of newly identified mutations in ion channels genes allowed to recognize new phenotypes and to widen the clinical spectrum of known diseases...
Mai 2020	[Electrophysiological features: The next precise step for SCN2A developmental epileptic encephalopathy] Pu Miaom, Siyang Tang, Jia Ye, Jianda Wang, Yuting Lou, Bijun Zhang, Xiaoxiao Xu, Xiaoquan Chen, Yuezhou Li, Jianhua Feng Background - To investigate the relationships among phenotypes, genotypes, and funotypes of SCN2A-related developmental epileptic encephalopathy (DEE). Methods - We enrolled five DEE patients with five de novo variants of the SCN2A. Functional analysis and pharmacological features of Nav1.2 channel protein expressed in HEK293T cells were characterized by whole-cell patch-clamp recording. Results - The phenotypes of c.4712T>C(p. I1571T), c.2995G>A(p.E999K), and c.4015A>G(p. N1339D) variants showed similar characteristics, including early seizure onset with severe to profound intellectual disability...

April 2020	[The neonatal SCN2A mutant channel mimics adult channel properties] *Grace K. Muller* The advancement of whole-genome and -exome sequencing has helped to identify de novo genetic alterations in patients with early-onset epilepsy encephalopathy (EOEE; Sugawara et al., 2001; Heron et al., 2002). However, the evidence that the mutations are indeed pathogenic or how they affect the protein biology and/or neuronal network has not always come hand-in-hand with the genetic discoveries. In a recent issue of JGP, Thompson et al. addressed this issue by determining the electrophysiological and neuronal effects of human mutations occurring in the voltage-activated NaV1.2 (SCN2A) sodium channel (Thompson et al., 2020)...
April 2020	[SCN2A channelopathies in the autism spectrum of neuropsychiatric disorders: a role for pluripotent stem cells?] *Karina A. Kruth, Tierney M. Grisolano, Christopher A. Ahern, Aislinn J. Williams* Efforts to identify the causes of autism spectrum disorders have highlighted the importance of both genetics and environment, but the lack of human models for many of these disorders limits researchers' attempts to understand the mechanisms of disease and to develop new treatments. Induced pluripotent stem cells offer the opportunity to study specific genetic and environmental risk factors, but the heterogeneity of donor genetics may obscure important findings. Diseases associated with unusually high rates of autism, such as SCN2A syndromes, provide an opportunity to study specific mutations with high effect sizes in a human genetic context and may reveal biological insights applicable to more common forms of autism...
April 2020	[Differential inhibition of human Nav1.2 resurgent and persistent sodium currents by cannabidiol and GS967] *Emily R. Mason, Theodore R. Cummins* Many epilepsy patients are refractory to conventional antiepileptic drugs. Resurgent and persistent currents can be enhanced by epilepsy mutations in the Nav1.2 channel, but conventional antiepileptic drugs inhibit normal transient currents through these channels, along with aberrant resurgent and persistent currents that are enhanced by Nav1.2 epilepsy mutations. Pharmacotherapies that specifically target aberrant resurgent and/or persistent currents would likely have fewer unwanted side effects and be effective in many patients with refractory epilepsy. This study investigated the effects of cannbidiol (CBD) and GS967 (each at 1 μM) on transient, resurgent, and persistent currents in human embryonic kidney (HEK) cells stably expressing wild-type hNav1.2 channels...

April 2020	Insufficient evidence for "autism-specific" genes *Scott M.Myers, Thomas D. Challman, Raphael Bernier, Thomas Bourgeron, Wendy K.Chung, John N. Constantino, Evan E. Eichler, Sebastien Jacquemont, David T. Miller, Kevin J. Mitchell, Huda Y. Zoghbi, Christa Lese Martin, David H. Ledbetter* Despite evidence that deleterious variants in the same genes are implicated across multiple neurodevelopmental and neuropsychiatric disorders, there has been considerable interest in identifying genes that, when mutated, confer risk that is largely specific for autism spectrum disorder (ASD). Here, we review the findings and limitations of recent efforts to identify relatively "autism-specific" genes, efforts which focus on rare variants of large effect size that are thought to account for the observed phenotypes...
March 2020	Sodium channel epilepsies and neurodevelopmental disorders: from disease mechanisms to clinical application *Andreas Brunklaus, Dennis Lal* Genetic variants in brain-expressed voltage-gated sodium channels (SCNs) have emerged as one of the most frequent causes of Mendelian forms of epilepsy and neurodevelopmental disorders (NDDs). This review explores the biological concepts that underlie sodium channel NDDs, explains their phenotypic heterogeneity, and appraises how this knowledge may inform clinical practice. We observe that excitatory/inhibitory neuronal expression ratios of sodium channels are important regulatory mechanisms underlying brain development, homeostasis, and neurological diseases. We hypothesize that a detailed understanding of gene expression, variant tolerance, location, and function, as well as timing of seizure onset can aid the understanding of how variants in SCN1A , SCN2A , SCN3A , and SCN8A contribute to seizure aetiology and inform treatment choice. We propose a model in which variant type, development-specific gene expression, and functions of SCNs explain the heterogeneity of sodium channel associated NDDs...

February 2020	[Biological concepts in human sodium channel epilepsies and their relevance in clinical practice] *Andreas Brunklaus, Juanjiangmeng Du, Felix Steckler, Ismael I. Ghanty, Katrine M. Johannesen, Christina Dühring Fenger, Stephanie Schorge, David Baez-Nieto, Hao-Ran Wang, Andrew Allen, Jen Q. Pan, Holger Lerche, Henrike Heyne, Joseph D. Symonds, Sameer M. Zuberi, Stephan Sanders, Beth R. Sheidley, Dana Craiu, Heather E. Olson, Sarah Weckhuysen, Peter DeJonge, Ingo Helbig, Hilde Van Esch, Tiffany Busa, Matthieu Milh, Bertrand Isidor, Christel Depienne, Annapurna Poduri, Arthur J. Campbell, Jordane Dimidschstein, Rikke S. Møller, Dennis Lal* Voltage-gated sodium channels (SCNs) share similar amino acid sequence, structure, and function. Genetic variants in the four human brain-expressed SCN genes SCN1A/2A/3A/8A have been associated with heterogeneous epilepsy phenotypes and neurodevelopmental disorders. To better understand the biology of seizure susceptibility in SCN-related epilepsies, our aim was to determine similarities and differences between sodium channel disorders, allowing us to develop a broader perspective on precision treatment than on an individual gene level alone...
February 2020	[Association of SCN1A, SCN2A and UGT2B7 polymorphisms with responsiveness to valproic acid in the treatment of epilepsy] *Yuan Lu, Quanping Su, Ming Li, Alimu Dayimu, Xiaoyu Dai, Zhiheng Wang, Fengyuan Che, Fuzhong Xue* The efficacy of valproic acid (VPA) varies widely in clinical treatment of epileptic patients. Our study is aimed at exploring a potential association between polymorphisms of SCN1A, SCN2A, and UGT2B7 genetic factors and VPA responses. Methods. In this observational study, a total of 114 epileptic patients only treated with VPA for at least 1 year were included to explore the genetic polymorphisms of drug responses (mean follow-up time: 3.68 +/- 1.78 years)...
February 2020	[Seeing through a forest of SCN2A gene variation] *Michele Solis, SFARI (Simons Foundation Autism Research Initiative)* On August 2–3, 2019, the FamilieSCN2A Foundation held their biennial SCN2A Professional and Family meeting, in Seattle, Washington. The gathering brought together 37 families of individuals with mutations in the SCN2A gene, 60 investigators, eight clinicians and five industry groups that conduct research and/or clinical work on conditions related to this genetic change...

February 2020	Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism *F. Kyle Satterstrom, Jack A. Kosmicki, Jiebiao Wang, Michael S. Breen, Silvia De Rubeis, Joon-Yong An, Minshi Peng, Ryan Collins, Jakob Grove, Lambertus Klei, Christine Stevens, Jennifer Reichert, Maureen S. Mulhern, Mykyta Artomov, Sherif Gerges, Brooke Sheppard, Xinyi Xu, Aparna Bhaduri, Utku Norman, Harrison Brand, Grace Schwartz, Rachel Nguyen, Elizabeth E. Guerrero, Caroline Dias, Catalina Betancur, Edwin H. Cook, Louise Gallagher, Michael Gill, James S. Sutcliffe, Audrey Thurm, Michael E. Zwick, Anders D. Børglum, Matthew W. State, A. Ercument Cicek, Michael E. Talkowski, David J. Cutler, Bernie Devlin, Stephan J. Sanders, Kathryn Roeder, Mark J. Daly, Joseph D. Buxbaum* We present the largest exome sequencing study of autism spectrum disorder (ASD) to date (n = 35,584 total samples, 11,986 with ASD). Using an enhanced analytical framework to integrate de novo and case-control rare variation, we identify 102 risk genes at a false discovery rate of 0.1 or less. Of these genes, 49 show higher frequencies of disruptive de novo variants in individuals ascertained to have severe neuro-developmental delay, whereas 53 show higher fre-quencies in individuals ascertained to have ASD; comparing ASD cases with mutations in these groups reveals phenotypic differences...
January 2020	Phenotypic spectrum and genetics of SCN2A‐related disorders, treatment options, and outcomes in epilepsy and beyond *Markus Wolff, Andreas Brunklaus, Sameer M. Zuberi* Pathogenic variants in the SCN2A gene are associated with a variety of neurodevelopmental phenotypes, defined in recent years through multicenter collaboration. Phenotypes include benign (self-limited) neonatal and infantile epilepsy and more severe developmental and epileptic encephalopathies also presenting in early infancy. There is increasing evidence that an important phenotype linked to the gene is autism and intellectual disability without epilepsy or with rare seizures in later childhood...
January 2020	SCN2A channelopathies: Mechanisms and models *Ulrike B. S. Hedrich, Stephan Lauxmann, Holger Lerche* Variants in the SCN2A gene, encoding the voltage-gated sodium channel NaV1.2, cause a variety of neuropsychiatric syndromes with different severity ranging from self-limiting epilepsies with early onset to developmental and epileptic encephalopathy with early or late onset and intellectual disability (ID), as well as ID or autism without seizures. Functional analysis of channel defects demonstrated a genotype-phenotype correlation and suggested effective treatment options for one group of affected patients carrying gain-of-function variants...

January 2020	The phenotypic spectrum of SCN2A-related epilepsy *Claire Reynolds, Mary D. King, Kathleen M. Gorman* Pathogenic variants in SCN2A are reported in a spectrum of neurodevelopmental disorders including developmental and epileptic encephalopathies, benign familial neonatal-infantile seizures, episodic ataxia, and autism spectrum disorder and intellectual disability with and without seizures. To date, more than 300 patients with SCN2A variants have been published, the majority presenting with epilepsy...
January 2020	Alternative splicing potentiates dysfunction of early-onset epileptic encephalopathy SCN2A variants *Christopher H. Thompson, Roy Ben-Shalom, Kevin J. Bender, Alfred L. George, Jr.* Epileptic encephalopathies are severe forms of infantile-onset epilepsy often complicated by severe neurodevelopmental impairments. Some forms of early-onset epileptic encephalopathy (EOEE) have been associated with variants in SCN2A, which encodes the brain voltage-gated sodium channel NaV1.2. Many voltage-gated sodium channel genes, including SCN2A, undergo developmentally regulated mRNA splicing. The early onset of these disorders suggests that developmentally regulated alternative splicing of NaV1.2 may be an important consideration when elucidating the pathophysiological consequences of epilepsy-associated variants...
October 2019	The genetic landscape of epilepsy of infancy with migrating focal seizures *Rosemary Burgess PhD, Shuyu Wang MBBS, BMedSci, Amy McTague PhD, Katja E. Boysen PhD, Xiaoling Yang MD, PhD, Qi Zeng MD, PhD, Kenneth A. Myers MD, PhD, Anne Rochtus MD, PhD, Marina Trivisano MD, PhD, Deepak Gill FRACP, EIMFS Consortium, Lynette G. Sadleir MBChB, MD, Nicola Specchio MD, PhD, Renzo Guerrini MD, FRCP, Carla Marini MD, Yue-Hua Zhang MD, PhD, Heather C. Mefford MD, PhD, Manju A. Kurian MBChB, PhD, Annapurna H. Poduri MD, MPH, Ingrid E. Scheffer MBBS, PhD* Epilepsy of infancy with migrating focal seizures (EIMFS) is one of the most severe developmental and epileptic encephalopathies. We delineate the genetic causes and genotype–phenotype correlations of a large EIMFS cohort...
September 2019	Resurgent and gating pore currents induced by de novo SCN2A epilepsy mutations *Emily R. Mason, Fenfen Wu, Reesha R. Patel, Yucheng Xiao, Stephen C. Cannon, Theodore R. Cummins* Over 150 mutations in the SCN2A gene, which encodes the neuronal Nav1.2 protein, have been implicated in human epilepsy cases. Of these, R1882Q and R853Q are two of the most commonly reported mutations. This study utilized voltage-clamp electrophysiology to characterize the biophysical effects of the R1882Q and R853Q mutations on the hNav1.2 channel, including their effects on resurgent current and gating pore current, which are not typically investigated in the study of Nav1.2 channel mutations...

August 2019	[The autism-associated gene SCN2A contributes to dendritic excitability and synaptic function in the prefrontal cortex] *Perry W.E. Spratt, Roy Ben-Shalom, Caroline M. Keeshen, Kenneth J. Burke Jr., Rebecca L. Clarkson, Stephan J. Sanders, Kevin J. Bender* Autism spectrum disorder (ASD) is strongly associated with de novo gene mutations. One of the most commonly affected genes is SCN2A. ASD-associated SCN2A mutations impair the encoded protein NaV1.2, a sodium channel important for action potential initiation and propagation in developing excitatory cortical neurons. The link between an axonal sodium channel and ASD, a disorder typically attributed to synaptic or transcriptional dysfunction, is unclear. Here we show that NaV1.2 is unexpectedly critical for dendritic excitability and synaptic function in mature pyramidal neurons in addition to regulating early developmental axonal excitability...
May 2019	[Parental mosaicism in epilepsies due to alleged de novo variants] *Rikke S. Møller, Nora Liebmann, Line H. G. Larsen, Mathias Stiller, Julia Hentschel, Nahrain Kako, Dalia Abdin, Nataliya Di Donato, Deb K. Pal, Pia Zacher, Steffen Syrbe, Hans A. Dahl, Johannes R. Lemke* Severe early onset epilepsies are often caused by de novo pathogenic variants. Few studies have reported the frequency of somatic mosaicism in parents of children with severe epileptic encephalopathies. Here we aim to investigate the frequency of mosaicism in the parents of children with epilepsy caused by alleged de novo variants. We tested parental genomic DNA derived from different tissues for 75 cases using targeted next-generation sequencing. Five parents (6.6%) showed mosaicism at minor allele frequencies of 0.8%-29% for the pathogenic variant detected in their offspring. Parental mosaicism was observed in the following genes: SCN1A, SCN2A, SCN8A, and STXBP1...
May 2019	[Clinical and genetic spectrum of SCN2A-associated episodic ataxia] *N. Schwarz, T. Bast, E. Gaily, G. Golla, K. M. Gorman, L. R. Griffiths, A. Hahn, J. Hukin, M. King, C. Korff, M. J. Miranda, R. S. Møller, B. Neubauer, R. A. Smith, T. Smo,l P. Striano, B. Stroud, M. Vaccarezza, G. Kluger, H. Lerche, W. Fazeli* Pathogenic variants in SCN2A are associated with various neurological disorders including epilepsy, autism spectrum disorder and intellectual disability. Few reports have recently described SCN2A-associated episodic ataxia (EA). Our study identifies its broader clinical and genetic spectrum, and describes pharmacological approaches...

March 2019	SCN2A haploinsufficient mice display a spectrum of phenotypes affecting anxiety, sociability, memory flexibility and ampakine CX516 rescues their hyperactivity *Tetsuya Tatsukawa, Matthieu Raveau, Ikuo Ogiwara, Satoko Hattori, Hiroyuki Miyamoto, Emi Mazaki, Shigeyoshi Itohara, Tsuyoshi Miyakawa, Mauricio Montal, Kazuhiro Yamakawa* Mutations of the SCN2A gene encoding a voltage-gated sodium channel alpha-II subunit Nav1.2 are associated with neurological disorders such as epilepsy, autism spectrum disorders, intellectual disability, and schizophrenia. However, causal relationships and pathogenic mechanisms underlying these neurological defects, especially social and psychiatric features, remain to be elucidated…
February 2019	Further corroboration of distinct functional features in SCN2A variants causing intellectual disability or epileptic phenotypes *Anaïs Begemann, Mario A. Acuña, Markus Zweier, Marie Vincent, Katharina Steindl, Ruxandra Bachmann-Gagescu, Annette Hackenberg, Lucia Abela, Barbara Plecko, Judith Kroell-Seger, Alessandra Baumer, Kazuhiro Yamakawa, Yushi Inoue, Reza Asadollahi, Heinrich Sticht, Hanns Ulrich Zeilhofer, Anita Rauch* Deleterious variants in the voltage-gated sodium channel type 2 (Nav1.2) lead to a broad spectrum of phenotypes ranging from benign familial neonatal-infantile epilepsy (BFNIE), severe developmental and epileptic encephalopathy (DEE) and intellectual disability (ID) to autism spectrum disorders (ASD). Yet, the underlying mechanisms are still incompletely understood...
January 2019	SCN1A and SCN2A polymorphisms are associated with response to valproic acid in Chinese epilepsy patients *Lihong Shi, Miaomiao Zhu, Huilan Li, Zhipeng Wen, Xiaoping Chen, Jia Luo, Cong Lin, Zanling Zhang* There is a large inter-individual variation in the efficacy of valproic acid (VPA) against epilepsy. The genetic polymorphism influence of sodium channels on VPA response remains a matter of debate. The aim of the study was to explore the effect of SCN1A and SCN2A gene polymorphisms on VPA response in the treatment of epilepsy among Chinese patients...

December 2018	Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies *The International League Against Epilepsy Consortium on Complex Epilepsies* The epilepsies affect around 65 million people worldwide and have a substantial missing heritability component. We report a genome-wide mega-analysis involving 15,212 individuals with epilepsy and 29,677 controls, which reveals 16 genome-wide significant loci, of which 11 are novel. Using various prioritization criteria, we pinpoint the 21 most likely epilepsy genes at these loci, with the majority in genetic generalized epilepsies. These genes have diverse biological functions, including coding for ion-channel subunits, transcription factors and a vitamin-B6 metabolism enzyme. Converging evidence shows that the common variants associated with epilepsy play a role in epigenetic regulation of gene expression in the brain...
August 2018	Relationship of electrophysiological dysfunction and clinical severity in SCN2A - related epilepsies *Stephan Lauxmann, Nienke E. Verbeek, Yuanyuan Liu, Mariana Zaichuk, Stephan Müller, Johannes R. Lemke, Marjan J.A. van Kempen, Holger Lerche, Ulrike B.S. Hedrich* Variants in the SCN2A gene cause a broad spectrum of epilepsy syndromes of variable severity including benign neonatal-infantile epilepsy (BFNIE), developmental and epileptic encephalopathies (DEE), and other neuropsychiatric disorders. Here, we studied three newly identified variants, which caused distinct phenotypes observed in nine affected individuals of three families, including BFNIE, and DEE with intractable neonatal seizures. Whole cell patch-clamp recordings of transfected tsA201 cells disclosed an increased current density and an increased subthreshold sodium inward current upon an action potential stimulus (p.(Lys908Glu)), a hyperpolarizing shift of the activation curve (p.(Val208Glu) and p.(Thr773Ile)), and an increased persistent current (p.(Thr773Ile))...
July 2018	Progress in understanding and treating SCN2A-mediated disorders *Stephan J. Sanders, Arthur J. Campbell, Jeffrey R. Cottrell, Rikke S. Moller, Florence F. Wagner, Angie L. Auldridge, Raphael A. Bernier, William A. Catterall, Wendy K. Chung, James R. Empfield, Alfred L. George Jr, Joerg F. Hipp, Omar Khwaja, Evangelos Kiskinis, Dennis Lal, Dheeraj Malhotra, John J. Millichap, Thomas S. Otis, Steven Petrou, Geoffrey Pitt, Leah F. Schust, Cora M. Taylor, Jennifer Tjernagel, John E. Spiro, Kevin J. Bender* Advances in gene discovery for neurodevelopmental disorders have identified SCN2A dysfunction as a leading cause of infantile seizures, autism spectrum disorder, and intellectual disability. SCN2A encodes the neuronal sodium channel NaV1.2. Functional assays demonstrate strong correlation between genotype and phenotype. This insight can help guide therapeutic decisions and raises the possibility that ligands that selectively enhance or diminish channel function may improve symptoms...

July 2018	Nonsyndromic intellectual disability with novel heterozygous SCN2A mutation and epilepsy *Takayuki Yokoi, Yumi Enomoto, Yoshinori Tsurusaki, Takuya Naruto, Kenji Kurosawa* SCN2A mutations are primarily associated with a variety of epilepsy syndromes. Recently, SCN2A has been reported as a gene responsible for nonsyndromic intellectual disability or autism spectrum disorders. Here, we present a case of a 12-year-old girl with nonsyndromic intellectual disability who exhibited a heterozygous de novo missense mutation in SCN2A. She developed seizures during the course of illness. This case suggests that the phenotype of patients with heterozygous SCN2A mutations can be variable...
May 2018	Dynamic action potential clamp predicts functional separation in mild familial and severe de novo forms of SCN2A epilepsy *Géza Berecki, Katherine B. Howell, Yadeesha H. Deerasooriya, Maria Roberta Cilio, Megan K. Oliva, David Kaplan, Ingrid E. Scheffer, Samuel F. Berkovic, Steven Petrou* SCN2A, encoding the voltage-gated sodium channel Nav1.2, has emerged as a major gene implicated in neonatal-, infantile-, and even childhood-onset epilepsies. Many of these epilepsies are also associated with cognitive and behavioral impairments that range in type and severity. The biophysical, neurophysiological, and clinical impacts of SCN2A mutations are poorly understood. Here, we use clinical evaluation and biophysical analyses to explore the mechanisms underpinning distinctive phenotypes produced by SCN2A variants associated with mild familial or severe de novo forms of epilepsy...
September 2017	Dravet syndrome and its mimics: Beyond SCN1A *Dora Steel, Joseph D. Symonds, Sameer M. Zuberi, Andreas Brunklaus* Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy characterized by the onset of prolonged febrile and afebrile seizures in infancy, and evolving to drug-resistant epilepsy with accompanying cognitive, behavioral, and motor impairment. Most cases are now known to be caused by pathogenic variants in the sodium channel gene SCN1A, but several other genes have also been implicated. This review examines current understanding of the role of non-SCN1A genes in DS, and what is known about phenotypic similarities and differences...

August 2017	Opposing effects on NaV1.2 function underlie differences between SCN2A variants observed in individuals with autism spectrum disorder or infantile seizures *Roy Ben-Shalom, Caroline M. Keeshen, Kiara N. Berrios, Joon Y. An, Stephan J. Sanders, Kevin J. Bender* https://www.youtube.com/watch?v=zzP3DZcViyY Variants in the SCN2A gene that disrupt the encoded neuronal sodium channel NaV1.2 are important risk factors for autism spectrum disorder (ASD), developmental delay, and infantile seizures. Variants observed in infantile seizures are predominantly missense, leading to a gain of function and increased neuronal excitability. How variants associated with ASD affect NaV1.2 function and neuronal excitability are unclear...
April 2017	Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders *Markus Wolff, Katrine M. Johannesen, Ulrike B. S. Hedrich, Silvia Masnada, Guido Rubboli, Elena Gardella, Gaetan Lesca, Dorothée Ville, Mathieu Milh, Laurent Villard, Alexandra Afenjar, Sandra Chantot-Bastaraud, Cyril Mignot, Caroline Lardennois, Caroline Nava, Niklas Schwarz, Marion Gérard, Laurence Perrin, Diane Doummar, Stéphane Auvin, Maria J. Miranda, Maja Hempel, Eva Brilstra, Nine Knoers, Nienke Verbeek, Marjan van Kempen, Kees P. Braun, Grazia Mancini, Saskia Biskup, Konstanze Hörtnagel, Miriam Döcker, Thomas Bast, Tobias Loddenkemper, Lily Wong-Kisiel, Friedrich M. Baumeister, Walid Fazeli, Pasquale Striano, Robertino Dilena, Elena Fontana, Federico Zara, Gerhard Kurlemann, Joerg Klepper, Jess G. Thoene, Daniel H. Arndt, Nicolas Deconinck, Thomas Schmitt-Mechelke, Oliver Maier, Hiltrud Muhle, Beverly Wical, Claudio Finetti, Reinhard Brückner, Joachim Pietz, Günther Golla, Dinesh Jillella, Karen M. Linnet, Perrine Charles, Ute Moog, Eve Õiglane-Shlik, John F. Mantovani, Kristen Park, Marie Deprez, Damien Lederer, Sandrine Mary, Emmanuel Scalais, Laila Selim, Rudy Van Coster, Lieven Lagae, Marina Nikanorova, Helle Hjalgrim, G. Christoph Korenke, Marina Trivisano, Nicola Specchio, Berten Ceulemans, Thomas Dorn, Katherine L. Helbig, Katia Hardies, Hannah Stamberger, Peter de Jonghe, Sarah Weckhuysen, Johannes R. Lemke, Ingeborg Krägeloh-Mann, Ingo Helbig, Gerhard Kluger, Holger Lerche, Rikke S Møller* Mutations in SCN2A, a gene encoding the voltage-gated sodium channel Nav1.2, have been associated with a spectrum of epilepsies and neurodevelopmental disorders. Here, we report the phenotypes of 71 patients and review 130 previously reported patients. We found that (i) encephalopathies with infantile/childhood onset epilepsies (≥3 months of age) occur almost as often as those with an early infantile onset (<3 months), and are thus more frequent than previously reported; (ii) distinct phenotypes can be seen within the late onset group, including myoclonic-atonic epilepsy (two patients), Lennox-Gastaut not emerging from West syndrome (two patients), and focal epilepsies with an electrical status epilepticus during slow sleep-like EEG pattern (six patients); and (iii) West syndrome constitutes a common phenotype with a major recurring mutation (p.Arg853Gln: two new and four previously reported children). Other known phenotypes include Ohtahara syndrome, epilepsy of infancy with migrating focal seizures, and intellectual disability or autism without epilepsy...

April 2016	Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis *Natalie Trump, Amy McTague, Helen Brittain, Apostolos Papandreou, Esther Meyer, Adeline Ngoh, Rodger Palmer, Deborah Morrogh, Christopher Boustred, Jane A Hurst, Lucy Jenkins, Manju A Kurian, Richard H Scott* Background - We sought to investigate the diagnostic yield and mutation spectrum in previously reported genes for early-onset epilepsy and disorders of severe developmental delay. Methods - In 400 patients with these disorders with no known underlying aetiology and no major structural brain anomaly, we analysed 46 genes using a combination of targeted sequencing on an Illumina MiSeq platform and targeted, exon-level microarray copy number analysis. Results - We identified causative mutations in 71/400 patients (18%). The diagnostic rate was highest among those with seizure onset within the first two months of life (39%), although overall it was similar in those with and without seizures. The most frequently mutated gene was SCN2A (11 patients, 3%)...
September 2015	SCN2A encephalopathy: A major cause of epilepsy of infancy with migrating focal seizures *Katherine B. Howell, Jacinta M. McMahon, Gemma L. Carvill, Dimira Tambunan, Mark T. Mackay, Victoria Rodriguez-Casero, Richard Webster, Damian Clark, Jeremy L. Freeman, Sophie Calvert, Heather E. Olson, Simone Mandelstam, Annapurna Poduri, Heather C. Mefford, A. Simon Harvey, Ingrid E. Scheffer* Objective: De novo SCN2A mutations have recently been associated with severe infantile-onset epilepsies. Herein, we define the phenotypic spectrum of SCN2A encephalopathy. Methods: Twelve patients with an SCN2A epileptic encephalopathy underwent electroclinical phenotyping...

June 2014	Differential Effects of Common Variants in SCN2A on General Cognitive Ability, Brain Physiology, and messenger RNA Expression in Schizophrenia Cases and Control Individuals *Dwight Dickinson, PhD; Richard E. Straub, PhD; Joey W. Trampush, PhD; et al* Importance - One approach to understanding the genetic complexity of schizophrenia is to study associated behavioural and biological phenotypes that may be more directly linked to genetic variation. Objective - To identify single-nucleotide polymorphisms associated with general cognitive ability (*g*) in people with schizophrenia and control individuals. Design, Setting, and Participants - Genomewide association study, followed by analyses in unaffected siblings and independent schizophrenia samples, functional magnetic resonance imaging studies of brain physiology in vivo, and RNA sequencing in postmortem brain samples. The discovery cohort and unaffected siblings were participants in the National Institute of Mental Health Clinical Brain Disorders Branch schizophrenia genetics studies. Additional schizophrenia cohorts were from psychiatric treatment settings in the United States, Japan, and Germany.
March 2004	A nonsense mutation of the sodium channel gene SCN2A in a patient with intractable epilepsy and mental decline *Kazusaku Kamiya, Makoto Kaneda, Takashi Sugawara, Emi Mazaki, Nami Okamura, Mauricio Montal, Naomasa Makita, Masaki Tanaka, Katsuyuki Fukushima, Tateki Fujiwara, Yushi Inoue, Kazuhiro Yamakawa* Mutations, exclusively missense, of voltage-gated sodium channel α subunit type 1 (SCN1A) and type 2 (SCN2A) genes were reported in patients with idiopathic epilepsy: generalized epilepsy with febrile seizures plus. Nonsense and frameshift mutations of SCN1A, by contrast, were identified in intractable epilepsy: severe myoclonic epilepsy in infancy (SMEI). Here we describe a first nonsense mutation of SCN2A in a patient with intractable epilepsy and severe mental decline. The phenotype is similar to SMEI but distinct because of partial epilepsy, delayed onset (1 year 7 months), and absence of temperature sensitivity. A mutational analysis revealed that the patient had a heterozygous de novo nonsense mutation R102X of SCN2A...