Table S1. Developmental disease-associated mutations intersect with calcium signaling.
Select genes from the SFARI Gene Database encode protein products that either directly regulate calcium homeostasis and signaling or indirectly impinge on calcium by modulating neuronal excitability or altering membrane potential. We restricted our survey to genes defined as either Category 1 (high confidence) or Category 2 (strong candidate) (see: https://gene.sfari.org/about-gene-scoring/ for the SFARI gene scoring criteria) and list the developmental functions of their gene products and the functional effects (when known) of select disease-associated mutations. This Table only highlights selected genes and is not exhaustive in scope. Notably, due to space constraints, we have not included synaptic structural proteins that regulate ion/calcium channel localization and function at synapses [e.g., ANK2 (Kline et al., 2014), NRXN1-3 (Luo et al., 2020; Missler et al., 2003)], which have been reproducibly implicated in ASD.

Gene	Mutation type	Disease	Relationship to calcium/activity dependent signaling	Electrophysiological characterization of select variants and/or select developmental phenotypes	References
CALCIUM CHANNELS					
ATP2B2	missense, nonsense, truncating variants,	ASD, epilepsy	encodes the PMCA2 ATPase calcium pump	> LoF mutations predicted to result in excess intracellular calcium; > ASD associated variants (e.g., Cys756*, Trp1064* - predicted to lead to nonsense mediated decay); > heterozygous LoF mice: heightened amplitude AMPAR-mediated calcium transients in cerebellar Purkinje cells; increased expression of P/Q-type VGCCs; increased amplitude depolarization-induced calcium influx, decreased Purkinje cell numbers; > KO mice: reduced growth rate, balance and movement problems, deafness and vestibular problems	***Select genetic studies:*** *Carayol et al. 2011; Takata et al., 2018; Iossifov et al. 2014; Yang et al., 2013; Prandini et al., 2012* ***Select functional references:*** *Smits et al., 2019; Fakira et al., 2012; Kozel et al., 1998*
CACNA1A	missense, frameshift, stop-gain and LoF variants	ASD, ID, epilepsy (e.g., EE, primary generalized epilepsy), paroxysmal movement disorders; FHM	encodes the pore forming subunit of the VGCC Cav2.1	> GoF mutations (e.g. R192Q mutation implicated in FHM): knock-in mice exhibit elevated calcium current density in cerebellar granule cells, increased neurotransmitter release at neuromuscular synapses, enhanced induction of cortical spreading depression; > epilepsy related mutations: dominant negative, impaired channel function (e.g. C5733T, E147K); > KO mice: ataxia, dystonia and early death, irregular corticothalamic activity; > interneuron-specific LOF: epilepsy, abnormal GABA release from PV+ cells; > pyramidal neuron specific LOF: attenuates excitability	***Select genetic studies:*** *Gulsuner et al., 2020; Epi4k Consortium 2016; Hamdan et al., 2017; Damaj et al., 2015; Jiang, 2015; Jouvenceau et al., 2001; Imbrici et al., 2004; Stam et al., 2009; commentary in Noebels et al., 2002* ***Select functional references:*** *Bomben et al., 2016; Rossignol et al., 2013; Llinás et al., 2007; Todorov et al., 2006; van den Maagdenberg et al., 2004; Kaja et al., 2005; commentary in Noebels et al., 2002*
CACNA1C	missense variants, G406R point mutation in *exon 8a*	classical TS, SCZ, BPD	encodes the pore forming subunit of the VGCC Cav1.2	> GoF TS mutation: impaired channel splicing, loss of voltage-dependent channel inactivation, increased depolarization-dependent calcium elevations, altered cortical projection neuron differentiation, activity-dependent dendritic retraction, deficits in cortical excitatory and inhibitory neuron migration	***Select genetic studies:*** *Splawski, et al. 2004; SCZ Psychiatric GWAS consortium 2011; Cross-disorder group of Psychiatric Genomics Consortium, 2013; SCZ Working Group of the Psychiatric Genomics Consortium, 2014; Ripke, et al. 2013; Ferreira et al, 2008; Purcell, et al. 2014, Green et al., 2010; Green et al., 2013* ***Select functional references:*** *Splawski, et al. 2004; Barrett & Tsien, 2008; Pasca et al., 2011; Krey et al., 2011; Birey et al., 2017; Kamijo et al., 2018; Panagiotakos et al., 2019; reviewed by Bhat et al., 2012*
CACNA1D	missense, LOF, and GoF variants	ASD, epilepsy	encodes the pore forming subunit of the VGCC Cav1.3	> GoF mutations: impaired/irregular voltage-dependent channel inactivation (e.g., G407R, G403D, G403R, Q547H, P1336R, A769G, V401L and S652L); hyperpolarized voltage dependence of activation (e.g., V259D, F747L, I750M, V1153G, A769G, V401L and S652L); increased current density (e.g. V401L); > LoF mutations: increased sensitivity to dihydropyridine inhibition (e.g. S652L); > ASD-associated mutation A760G: reduced calcium dependent inactivation, altered channel gating leading to increased intracellular calcium > KO mice: deafness, cardiac irregularities	***Select genetic studies:*** *O'Roak et al., 2012; Klassen et al., 2011* ***Select functional references:*** *Pinggera et al., 2015, 2017, 2018; Hofer et al., 2020; reviewed by Ortner et al., 2020; Baig et al. 2011; Scholl et al. 2013; Limpitikul et al., 2016; Platzer et al., 2000*
CACNA1E	missense, synonymous, and GoF/LoF variants	ASD, DEE	encodes the pore forming subunit of the VGCC Cav2.3	> G1209S: top de novo ASD risk mutation; > GoF mutations: slow inactivation, hyperpolarizing shifts in voltage dependent activation, increased current density (e.g. majority of DEE variants in pore domains, S6 variants: F698S, I701V, A702T; S4-5 variant: I603L); > KO mice: CA1 pyramidal cells from KO mice exhibit increased excitability, and altered action potential properties; neurons of the reticular thalamus have significantly reduced high voltage activated calcium currents, and suppressed rhythmic burst discharges.	***Select genetic studies:*** *O'Roak et al., 2012; Takata et al., 2016; Helbig et al., 2018; comment in Carvill et al., 2019; Neale et al., 2012* ***Select functional references:*** *Helbig et al., 2018, Zaman et al., 2011, Neale et al., 2012; comment in Carvill et al., 2019; Gutzman et al., 2019*
CACNA1H	missense and LoF/GoF variants	ASD, epilepsy (e.g. CAE)	encodes the pore forming subunit of the VGCC Cav3.2	> missense LoF ASD mutations in voltage sensor (e.g., R212C, R902W), pore-forming domains (e.g., W962C), and c-terminus (e.g., R1871Q + A1874V): significantly reduced Cav3.2 (T-type) calcium currents; > CAE associated variants result in GoF and LoF (e.g., C456S, G773D, R788C, V831M, E282K: altered voltage dependence of activation; F161L, P648L, G773D, R788C: altered voltage dependence of inactivation; C456S, A748V, D1463N: faster activation kinetics; G773D, G784S, R788C, V831M: slower activation kinetics; F161L: faster inactivation kinetics; G499S, P648L, G773D, R788C, V831M, G773D, V831M, G848S, R788C, G773D, R788C: slower inactivation/deactivation kinetics); > modeling predicts net GOF/enhanced burst firing of thalamic neurons for CAE associated variants (e.g., C456S, P648L, G773D, R788C, G773D-R788C, A748V, G784S, G848S, and D1463N); > modeling predicts decreased thalamic neuron burst firing for CAE associated variants (e.g., E282K and V831M); > KO mice have anxiety-like phenotypes and impairments in memory	***Select genetic studies:*** *Chen et al., 2003; Splawski et al., 2006; Vitko et al., 2005; Heron et al., 2007* ***Select functional references:*** *Khosravani et al., 2004; reviewed by Perez-Reyes 2006; Vitko et al., 2005; Vitko et al., 2007; Heron et al., 2007; Gackiere et al., 2008, Tao et al., 2008; Becker et al., 2008; Powell et al., 2009; Hu et al., 2009; Gangarossa et al., 2014; Splawski et al., 2006*
CACNA2D3	missense variants, splice site mutations, deletions	ASD, epilepsy	encodes the auxiliary α2δ3 VGCC subunit	> deletion of *CACNA2D3* homolog *unc-36* in c-elegans: altered axon termination; > *Cacna2d3* KO mice: impaired hearing, increased anxiety-related behaviors, reduced sensitivity to thermal pain	***Select genetic studies:*** *Iossifov et al., 2012; Girirajan et al., 2013; De Rubeis et al., 2014; C Yuen et al., 2017* ***Select functional references:*** *Buddell et al., 2019; Peng et al., 2021; Landmann et al., 2019; Pirone et al., 2014; Neely et al., 2010*
CACNB2	various missense variants	ASD	encodes the auxiliary β2 VGCC subunit	> GoF ASD-associated mutations (e.g., G167S, S197F): slower time dependent inactivation, altered sensitivity of voltage dependent inactivation, enhanced peak current densities; > LoF ASD-associated mutations (e.g., F240L): accelerated time-dependent inactivation	***Select genetic studies:*** *Cross disorder group of the psychiatric genomics consortium 2013; Ripke et al., 2013; Cross disorder group of the psychiatric genomics consortium 2017; Pardinas et al., 2018, Yuen et al., 2015* ***Select functional references:*** *Breitenkamp et al., 2014; Graziano et al, 2021; Despang et al., 2020*
TRPC6	translocations, missense variants, premature stop variant	ASD	encodes a calcium permeable cation channel from the transient receptor potential family	> neural progenitor cells from ASD patient-derived iPSCs: reduced calcium influx; > neurons from ASD patient-derived iPSCs: reduced TRPC6 protein levels, reduced dendritic spine density, altered synaptic properties; > transgenic *Trpc6* GOF: increased dendritic spine density, enhanced spatial memory	***Select genetic studies:*** *Griesi-Oliveira et al., 2014* ***Select functional references:*** *Griesi-Oliveira et al. 2015; Zhou et al., 2008*
TRPM1	CNVs, deletions	ASD	encodes a calcium permeable cation channel from the transient receptor potential family	> *Trpm1* KO mice: hyperactive, attenuated anxiety-related behaviors, altered fear memory, abnormal social behavior	***Select genetic studies:*** *Girirajan et al., 2013; Matsunami et al., 2014* ***Select functional references:*** *Hori et al., 2021*
OTHER ION CHANNELS THAT IMPINGE ON CALCIUM ENTRY AND ACTIVITY DEPENDENT SIGNALING					
CHRNA7	copy number variants, missense variants, microdeletion	Epilepsy, SCZ, DD, ID, ASD	encodes a calcium permeable nicotinic cholinergic receptor	> KO mice: phenotypes dependent on background strain due to differences in endogenous *Chrna7*; > C3H KO mice: impaired LTP, abnormal auditory processing; > C3H Het mice: reduced GAD65 levels, reduced GABAA receptors in male mice; > reduced *CHRNA7* transcription and function (e.g., *CHRNA7* promoter variants); decreased calcium influx through CHRNA7 (e.g., both 15q13.3 deletions and duplications); increased ER stress (e.g., 15q13.3 duplications)	***Select genetic studies:*** *Mikhail et al., 2011; Shinawi et al,. 2009; Soler-Alfonso et al., 2014; Gillentine et al., 2017; Hoppman-Chaney et al., 2013; Leonard et al., 2002; Gault et al., 2003; Stephens et al., 2009* ***Select functional references:*** *Yin et al., 2017; Freund et al., 2016; Adams et al., 2012; Leonard et al., 2002; Sinkus et al., 2011; Gillentine et al., 2017*
KCNJ10	missense variants, synonymous variants, LoF/GoF variants	Seizures, ASD	encodes an ATP-sensitive potassium channel	> KO mice: motor impairments, hypomyelination, axonal abnormalities, retarded growth, dehydration, abnormalities in renal salt handling, premature death; > astrocyte- and oligodendrocyte-specific cKO: seizures, premature death, ataxia, hindleg paralysis, retarded growth, abnormal astrocyte depolarization, impaired uptake of glutamate and potassium, reduced spontaneous neuronal activity, abnormalities in post-tetanic potentiation and short-term potentiation; > oligodendrocyte-specific cKOs: mitochondrial abnormalities, axonal degeneration, loss of axonal integrity, neuronal loss, visual deficits, retinal abnormalities, motor problems, functional abrnomalities including slow potassium clearance, delayed axonal recovery post stimuation, seizures; > GoF mutations: enhanced membrane expression; increased current density (e.g., R18Q); pH-dependent current inhibition (e.g., R348H); increased current amplitudes (e.g., R18Q, V84M); increased unit conductance (e.g. V84M); > homozygous missense mutations affecting transmembrane domain (e.g., G65P, G77R) modeled in *Xenopus*: decreased potassium currents	***Select genetic studies:*** *Ferraro et al.,2004; Buono et al., 2004; Sicca et al., 2011; Bockenhauer et al., 2009* ***Select functional references:*** *Bockenhauer et al., 2009; Neusch et al., 2001; Djukic et al., 2007; Schirmer et al., 2018; Larson et al., 2018; Sicca et al., 2011*
KCNMA1	missense variant, frame shift variant, GoF variants, LoF variant	Epilepsy, ASD, paroxysmal dyskinesia	encodes the pore-forming α-subunit of the large conductance calcium and voltage-activated potassium channel	> LoF mutations: altered resting membrane potential, decreased channel activity; > KO mice: alterations in suprachiasmatic nucleus function and circadian rhythm, progressive hearing loss, cerebellar abnormalities, motor coordination dysfunction, reduced activity of Purkinje neurons, dysfunctional astrocyte/arteriolar smooth muscle communication; > GoF mutations: enhanced voltage dependent activation and enhanced voltage sensitivity (e.g. N536H); in *Xenopus* oocytes: increased voltage- and calcium-dependent activation, faster activation kinetics in response to depolarizing voltage (e.g., D434G mutation); in CHO cells: increased sensitivity to calcium, activation at lower voltages, increase in open-channel probilitity (e.g., D434G)	***Select genetic studies:*** *Laumonnier et al., 2006; Neale et al., 2012; Liang et al., 2019; Zhang et al., 2020b; Satterstrom et al., 2020; Zou et al., 2021; Bailey et al., 2019; Du et al., 2005; Tabarki et al., 2016; Zhang et al., 2015* ***Select functional references:*** *Plüger et al., 2000; Díez-Sampedro et al., 2006; Meredith et al., 2006; Ruttiger et al., 2004; Sausbier et al., 2004; Filosa et al., 2006; Zhang et al., 2020b; Du et al., 2005*
GRIA2	nonsense variant, missense variant, deletions	ASD, ID, seizures, DEE, DD	encodes the GluA2 AMPAR subunit, whose inclusion in AMPARs renders them calcium-impermeable	> LoF mutations: decrease current amplitudes compared to wild type (WT) channels (e.g., G47E, D302G, del528-530, G609R, A639S, F644L, T646N); > GoF mutations: increase current amplitudes compared to WT channels (e.g., Q607E); > KO mice: increased calcium permeability in hippocampal neurons lacking GluA2, alterations in LTP, impaired exploratory behavior, alterations in reward behaviors	***Select genetic studies:*** *De Rubeis et al., 2014; Deciphering Developmental Disorders Study 2017; C Yuen et al., 2017; Hackmann et al., 2012* ***Select functional references:*** *Salpietro et al., 2019; Lu et al., 2009; Jia et al., 1996; Hackmann et al., 2012; Mead et al., 2003*
GRIN1	missense variants	ASD, Polymicrogyria, Epilepsy, ID, DD	encodes the GluN1 subunit of calcium permeable NMDARs	> LoF missense variants in or adjacent to a transmembrane domain (e.g., P557R, S560dup, G618R, G620R, Y647S, G815R, F817L, Q556*, G827R); > GoF mutations: increased calcium currents through NMDARs (e.g., E662K); > *Grin1* KO mice: significantly attenuated NMDA-induced calcium rises, abnormal social behaviors; > *in utero* knockdown in developing cortex: deficits in radial migration; > conditional *Grin1* deletion in PV+ cells: reduced LTP induction and maintenance, impaired social behavior; > interneuron-specific *Grin1* deletion: attenuated NMDA currents; > conditional *Grin1* deletion in pyramidal cells: increased social approach behavior; > *Dlx5/6*-Cre mediated deletion *in utero*: abnormal morphological maturtion of Re+ interneurons and improper circuit integration	***Select genetic studies:*** *Epi4K Consortium et al., 2013; Hamdan et al, 2011; Jiang, 2015* ***Select functional references:*** *Hamdan et al, 2011; Gandal et al., 2012; Saunders et al., 2013; Lemke et al. 2016; commentary in Lemke, 2020; Forrest et al., 1994; Ferri et al., 2020; Billingslea et al., 2014; De Marco Garcia et al., 2015; Fry et al., 2018; reviewed by Vieira et al,. 2021*
GRIN2A	copy number variants, nonsense mutation, chromosome translocation breakpoints, missense variant	ASD, various epileptic syndromes (e.g., Landau-Kleffner syndrome, EE, childhood epilepsy, infantile onset EE), polymicrogyria, SCZ	encodes the GluN2A subunit of calcium permeable NMDARs	> GoF mutations: increased GluN1/GluN2A current density (e.g., R1067W); increased sensitivity to glutamate and/or glycine agonists (e.g., P552R, M817V, L812M, V452M, K669N, N447K, V506A, P699S); decreased magnesium block, increased current density (e.g., N447K); impaired zinc inhibition, normal current amplitude, glutamate and glycine affinities and open-state probabilities (e.g., A243V); increased total surface expression (e.g., K590N, K879R, R1067W); > LoF mutations (e.g., R518H, T531M, D731N, V685G, G483R, A716T, C436R, C231Y, A548T, P79R, I694T, M705V, A727T, V734L, K772E, R370W); loss of magnesium block and decreased calcium permeability (e.g., N615K); > *Grin2A* KO mice: altered NMDA/AMPA receptor currents in hippocampal neurons, impairments in LTP and LTD, increased locomotion, deficits in fear conditioning; > *in utero* knock down: no effect of cortical radial migration	***Select genetic studies:*** *Barnby et al., 2005; Endele et al 2010; Lemke et al., 2013; Yoo et al., 2012; Liu et al., 2021; Singh et al., 2022* ***Select functional references:*** *Liu et al., 2021; Endele et al 2010; Strehlow et al., 2019; Kannagara et al., 2015; Sakimura et al. 1995; Kiyama et al. 1998; Chen et al., 2017; Ogden et al., 2017; Yuan et al., 2014; Marwick et al., 2019; Bertocchi et al., 2021; Xu et al., 2018; Swanger et al., 2016; Gao et al., 2017; Addis et al., 2017; Serraz et al., 2016; reviewed by Vieira et al., 2021*
GRIN2B	splice site variants, non-synonymous variants, LoF variants, *GRIN2B* GoF (West syndrome), chromosome translocation breakpoints, frameshift mutations, missense mutations,	ASD, SCZ, West Syndrome, ID, DD, Epilepsy	encodes the GluN2B subunit of calcium permeable NMDARs	> GoF mutations: loss of voltage dependent magnesium block (e.g., N615I, V618G); reduced calcium permeability (e.g., N615I); > LoF GluN2B-724 truncation mutant: attenuated calcium influx, impaired trafficking to cell membrane, impaired dendritic morphogenesis; > LoF mutations: mutation in ligand binding domain, impaired glutamate binding, higher glutamate concentrations required for activation (e.g., G689S, G689C), poor expression of G689C variant at cell membrane; overexpression in hippocampal neurons: decreased frequency of NMDAR-dependent mEPSCs with faster deactivation kinetics, no change in frequency of AMPAR-dependent mEPSCs; > KO GluN2B to GluN2A "replacement" mouse: altered synaptic plasticity/development, reduced social exploration, hyperlocomotion; > MADM-mediated *Grin2b* KO: impaired dendritic pruning and patterning in DG granule cells and spiny stellate cells; > Dlx5/6-Cre mediated *Grin2b* deletion: abnormal morphological maturation of Re+ interneurons > GluN2B overexpression in mice: altered synaptic function, enhanced memory/learning	***Select genetic studies:*** *De Rubeis et al., 2014; Iossifov et al., 2015; Ohtsuki et al., 2001; Myers et al., 2011; Lemke et al., 2014; Epi4K Consortium et al., 2013; Endele et al., 2010; Zhao et al.,2011; Tarabeux et al., 2011; O'Roak et al., 2011; O'Roak et al., 2012; Kellner et al., 2021* ***Select functional references:*** *Lemke et al., 2014; Swanger et al., 2016; Tang et al., 1999; Freunscht et al., 2013; Fedele et al., 2018; Akashi et al,. 2009; Wang et al., 2009; Wang et al., 2011; Kellner et al., 2021; Bahry et al., 2021; Sceniak et al., 2019; De Marco Garcia et al., 2015; Jiang et al., 2015a; Espinosa et al., 2009; reviewed by Vieira et al., 2021*
GABRB2	missense variants, LoF mutations	ASD, epilepsy (e.g., CAE, DEE, EME)	encodes the β2 subunit of the GABAA receptor, activation elicits calcium influx in cortical NSPCs	> LoF disease-associated variants in N-terminal and transmembrane regions: reduced GABA-induced current amplitudes (e.g., I246T, V282A, I288S, P252L); > *Gabrb2* KO mice: increased susceptibility to seizures and epilepsy, altered startle response, reduced anxiety/depression behaviors, hyperlocomotivity, social behavioral abnormalities, memory deficits	***Select genetic studies:*** *Srivastava et al., 2014b; Iossifov et al. 2014; Satterstrom et al., 2020; Yang et al., 2020; Hamdan et al., 2017* ***Select functional references:*** *el Achkar et al, 2021; Yeung et al., 2018*

GABRB3	de novo LoF mutations, missense mutations, intronic variants, synonymous mutations	ASD, epilepsy (e.g., CAE)	encodes the β3 subunit of the GABAA receptor; activation elicits calcium influx in cortical NSPCs	> LoF CAE variants: reduced current densities compared to wild type channels (e.g., P11S, S15F, G32R); reduced peak current amplitudes and reduced surface expression (e.g., P11S)	***Select genetic studies:*** *Epi4K Consortium et al., 2013; Chen et al., 2014; De Rubeis et al., 2014; Yang et al., 2017; Urak et al., 2006; Tanaka et al., 2008; Sanders et al., 2015; Jiang, 2015* ***Select functional references:*** *Delahanty et al., 2012; Urak et al., 2006; Tanaka et al., 2008; Tanaka et al., 2012*
KCNB1	LoF mutations, missense mutation, nonsense variant	DD, epilepsy (e.g., EE, West Syndrome), ASD	encodes the voltage-gated potassium channel Kv2.1	> V378A: altered subcellular localization, altered electrophysiological properties (retained voltage dependent activation with faster inactivation kinetics), altered ion selectivity; > EE-associated mutations (e.g. S347R, G379R, T374I): deficits in ion selectivity; > epilepsy-associated mutations (e.g. R306C, G401R): R306C - altered voltage sensitivity, reduced neuronal firing; G401R - dominant negative mutation in channel pore, G401R abolishes Kv2.1 currents and reduces neuronal firing; > *Kcnb1* KO mice: hyperactivity, abnormalities in spatial learning, accelerated progression of seizures	***Select genetic studies:*** *de Kovel et al., 2017; Torkamani et al., 2014; Parrini et al., 2017; Thiffault et al., 2015; Srivastava et al., 2014a; Allen et al., 2016; Saitsu et al., 2015* ***Select functional references:*** *Torkamani et al., 2014; Thiffault et al., 2015; Speca et al., 2014; Saitsu et al., 2015*
KCNQ2	splice site variant, LoF mutations, missense variants, frameshift variants	ASD, BPD, epilepsy (e.g. DEE, benign familial neonatal seizures)	encodes the voltage gated potassium channel Kv7.2	> LoF mutations largely implicated in BFNS; > voltage sensor S4 transmembrane segment mutations: impaired channel function, dominant negative effect at subthreshold voltages, depolarizing shift in activation curve (e.g., I205V and R213Q); reduced current amplitudes, increased channel protein levels (e.g., R213Q); > pore forming S5 and S6 domain mutations: impaired channel function, dominant negative (e.g., A265P, T274M, G290D); > c-terminal mutations: reduced potassium current amplitude (e.g., R532W, M518V); > *Kcnq2* heterozygous null mice (modeling LoF pathogenic mutations): increased susceptibility to seizures and behavioral abnormalities including reduced sociability and hyperactivity; > homozygous null *Kcnq2* LOF: increased pyramidal neuron excitability	***Select genetic studies:*** *Singh et al., 1998; Jiang et al., 2013; Milh et al., 2013; Judy et al., 2013, Borsotto et al., 2007; Lee et al., 2019; Jiang, 2015* ***Select functional references:*** *Biervert et al., 1998; Borsotto et al., 2007, Zhang et al., 2020a; Soh et al., 2014; Orhan et al., 2014*
KCNQ3	translocation mutations, missense variant	ASD, epilepsy (e.g., benign familial neonatal seizures)	encodes the voltage gated potassium channel Kv7.3	> LoF variants largely implicated in BFNS; > GoF mutations linked to ASD and DD: channel GOF, not associated with seizures in patients (e.g., R230C, R230H, R230S, R227Q); voltage sensor mutations (e.g., R227 and R230); > LoF mutations: voltage sensor mutations (e.g., M240R; homomeric channels not functional, mutation affects voltage sensitivity, predicted increase in channel resting state stability and destabilization of active state); significantly reduced current density, impaired channel function (e.g., R330L, R330C)	***Select genetic studies:*** *Hirose et al., 2000; Epi4K Consortium et al., 2013; Miceli et al., 2020; Grinton et al.,2015; Gilling et al., 2013; Charlier et al., 1998* ***Select functional references:*** *Miceli et al., 2015; Miceli et al., 2020; Gilling et al., 2013; Sands et al., 2019*
P2RX5	gene disrupting mutations, LoF variants	ASD	encodes a calcium permeable purinergic receptor	unknown?	***Select genetic studies:*** *Sanders et al., 2015; Iossifov et al. 2014* ***Select functional references:*** *Bo et al., 2003*
SCN1A	protein truncation mutations (LoF), frameshift, nonsense, splice-donor, missense mutations	Asperger Syndrome, ASD, FHM, epilepsy (Dravet Syndrome, Severe myoclonic epilepsy of infancy, GEFS+)	encodes the α subunit of the voltage-gated sodium channel Nav1.1	> *SCN1A* LoF mutations: Dravet syndrome; > LoF mutations: reduced current amplitude, hypersensitivity to steady-state inactivation (e.g., S1328P); abolished sodium currents in HEK cells (e.g., E78X, W384X, E1587K, and R1596C); partial LOF, abnormal recovery after inactivation, reduced sodium current density (e.g., E788K and M909K); slow inactivation recovery, hyperpolarizing shifts in activation/inactivation (e.g., D249E); reduced current density, slow recovery after inactivation (e.g., T1934I), slow recovery from inactivation (e.g., E78D); > interneurons from iPSCs derived from individuals with Dravet Syndrome (heterozygous S1328P mutations): sodium current and AP firing deficits; no electrophysiological abnormalities in excitatory neurons; > mutations causing GEFS+ mainly missense mutations; > select mutations linked to GEFS+ (functional effects influenced by cell type/expression system): increased Nav1.1 channel function in HEKs (D188V), increased Nav1.1 function in *Xenopus* oocytes (W1204R, R1648H, D1866Y); decreased Nav1.1 channel function in *Xenopus* oocytes (R859C, T875M); decreased Nav1.1 channel function in tsA201 (V1353L, I1656M, R1657C, A1685V); > LoF in mice: epileptic seizures	***Select genetic studies:*** *Weiss et al. 2003; Escayg et al., 2000; Barela et al., 2006; Epi4K Consortium et al., 2013; Claes et al., 2001; Osaka et al., 2007; O'Roak et al., 2011; O'Roak et al., 2012; De Rubeis et al., 2014; C Yuen et al., 2017; Hamdan et al., 2017; Jiang et al., 2015b; Kluckova et al., 2020* ***Select functional references:*** *Weiss et al., 2003; Sun et al., 2016; Ogiwara et al., 2007; Barela et al., 2006; reviewed by Escayg and Goldin, 2010; Kluckova et al., 2020*
SCN2A	LoF variants (often associated with ASD), missense variants, GoF variants, protein truncating variants (ASD)	ASD, ID, epilepsy (infantile EE, benign infantile seizures), SCZ	encodes the α subunit of the voltage gated sodium channel Nav1.2	> Effects of mutations differ in mature and immature neurons owing to changes in subcellular distribution and splicing; > LoF mutations: often associated with ASD and ID, impaired excitability in immature neurons and altered dendritic dendritic excitability in mature neurons; > GoF mutations: mostly associated with infantile epilepsies, increased neuronal excitability; > K1422E: mutation in selectivity filter, renders channel calcium permeable; > R1902C: ASD-associated mutation, allows calcium-dependent conformational change in Nav1.2 when complexed with CaM; > homozygous KO mice: perinatal lethality; > heterozygous *Scn2a* LoF mice: impaired excitability and action potential initiation in immature neurons; impaired dendritic excitability and disrupted synaptic function and plasticity in mature neurons, with presence of immature dendritic spines; normal PV and SST neuron APs; hyperactivity, absence-like seizures, and learning delays	***Select genetic studies:*** *Hamdan et al., 2017; Jiang et al., 2015b; Sanders et al., 2012; Tavassoli et al., 2014; Jiang et al., 2013; Sundaram et al., 2013; Carroll et al., 2016* ***Select functional references:*** *Begemann et al., 2019; Spratt et al., 2019; Spratt et al., 2021; Zhang et al., 2021; Ben-Shalom et al., 2017; Heinemann et al., 1992; Echevarria-Cooper et al., 2022; Fromer et al., 2014; Kim et al., 2004; reviewed by Sanders et al., 2018*
SCN8A	various missense mutations	ASD, DD, ID, epilepsy (e.g. E1EE13)	encodes the voltage-gated α8-subunit of the sodium channel Nav1.6	> majority of patient mutations are GoF: increased channel activity due to alterations in opening and inactivation kinetics; > LoF mutations: cognitive impairment, movement disorders; > GoF mutations: heterozygous missense, increased neuronal excitability in postnatal rat hippocampal neuronal cultures (e.g., N1768D); enhanced channel activation in neurons in vitro, increased excitabillity and spontaneous activity (e.g., T767I); altered voltage dependence of activation, predicted to yield premature neuronal firing (e.g., N984K); > heterozygous knock-in N1768D mice: seizures and sudden unexpected death in Epilepsy, dose dependent effects (homozygous knock-in mice: earlier onset of seizures and death); > LoF mutations: abolishes sodium currents (e.g., G964R, E1218K); reduces protein abundance (e.g., E1218K); significantly reduced channel activity in HEKs, protein product stable and expressed at similar levels to WT, possible off target effects of mutant protein product (e.g., G1451S); > *in vitro* LoF but possible *in vivo* GoF (e.g, R223G: reduced current density and at 37C reduces protein stability; similar activation/inactivation kinetics as WT at 30C with increased ramp current - possible GoF > Conditional *Scn8a* deletion in inhibitory cells using Dlx5/6-Cre: absence epilepsy; no absence seizures with excitatory neuron-specific deletion	***Select genetic studies:*** *Epi4K Consortium et al., 2013; Veeramah et al., 2012; Blanchard et al., 2015; Estacion et al., 2014; de Kovel et al., 2014* ***Select functional references:*** *Veeramah et al., 2012; Wagnon et al., 2015; Blanchard et al., 2015; Estacion et al., 2014; Wagnon and Meisler 2015; de Kovel et al., 2014; Makinson et al., 2017*
SLC6A1	truncating variants, missense variants, splice site variants CNVs, insertions, deletions and synonymous variants, nonsense variant	epilepsy (myoclonic atonic, genetic generalized, non-acquired focal, Lennox-Gastaut syndrome), DD, ASD, ID, speech delay, SCZ	encodes the voltage-dependent GABA transporter protein type 1 responsible for sodium-dependent GABA reuptake	> LoF mutations associated with Lennox-Gastaut syndrome: reduced total protein levels in HEKs and rat cortical neurons, reduced cell surface expression, impaired GABA uptake (e.g., G234S); > P361T: heterozygous LoF mutation associated with epilepsy and autism, lower total protein levels, mutant protein abnormally localized in ER, reduced protein function and surface expression; > KO mice: homozygous LoF yields increased tonic inhibition, reduced phasic inhibition, reduced quantal GABA release, no change in GABA receptor density, tremor, walking abnormalities, decreased strength, seizures, and anxious behaviors; heterozygous LoF yields diminished GABA reuptake	***Select genetic studies:*** *Sanders et al., 2012, Satterstrom et al., 2020, Satterstrom et al., 2019; Cai et al., 2019; Carvill et al., 2015; Rees et al., 2020; Wang et al., 2020* ***Select functional references:*** *Cai et al., 2019; Carvill et al., 2015; Jensen et al., 2003; Cope et al., 2009; Chiu et al., 2005*
SELECT CALCIUM-INTERACTING PROTEINS, CALCIUM SIGNALING MODULATORS, AND ACTIVITY-DEPENDENT PROTEINS					
CREBBP	coding variants, point mutations, deletion, duplications, frameshift mutation, missense mutations, splice site mutations	ASD, Rubinstein-Taybi syndrome	encodes the calcium regulated transcriptional coactivator CBP, a CREB co-factor critical for activity-dependent gene expression	> CH1 domain mutant mice: deficits in social interaction, ASD-relevant repetitive behaviors, hyperactivity, and abnormal synaptic plasticity; > *Gfap*-cre mediated cKO mice: microcephaly, behavioral anomalies, reduced embryonic NSPC proliferation, deficits in NSPC migration, impaired postnatal neurogenesis, and abnormal pyramidal cell morphology	***Select genetic studies:*** *Petrij et al., 1995; Roelfsema et al., 2005; Barnby et al., 2005; Wincent, et al. 2016; Coupry et al., 2002* ***Select functional references:*** *Merk et al., 2018; Zheng et al., 2016; Schoof et al., 2019; Valor et al., 2011*
CASK	missense variants, splice site variant, premature stop variants	ASD	encodes a calcium/calmodulin-dependent serine protein kinase	> iPSC-derived neurons from *CASK* mutation carriers: reduced CASK levels, alterations in presynaptic development, reduced spontaneous calcium events; > neurons from *Cask* KO mice: increased frequency of spontaneous excitatory miniature synaptic events, decreased frequency of spontaneous inhibitory miniature synaptic events	***Select genetic studies:*** *Iossifov et al., 2014; Najm et al. 2008; Stessman et al. 2017; Becker et al., 2020; Mukherjee et al., 2020* ***Select functional reference:*** *Atasoy et al., 2007; Becker et al., 2020*
CIB2	copy number variants	ASD	encodes a calcium binding protein that mediates calcium signaling processes	> *Cib2* KO mice: hearing loss, loss of auditory hair cell currents; > CIB2 down regulation in zebrafish and *Drosophila*: deafness and vision deficits	***Select genetic studies:*** *Prasad et al., 2012; Riazuddin et al., 2012* ***Select functional references:*** *Wang et al., 2017; Riazuddin et al., 2012*
DYRK1A	truncating variants, nonsense mutations, missense variants, frameshift mutations, splice site variants, copy number variants (DS), translocation	ASD, ID, microcephaly, DD	encodes a kinase that regulates localization and/or activity of calcium-dependent transcription factors (e.g. NFAT, CREB)	> *DYRK1A* in Down syndrome (DS) critical region, copy number increase implicated in DS; > LoF *DYRK1A* mutations: microcephaly, ID and ASD; > kinase domain mutations alter catalytic activity; R467Q: predicted function in protein stability; L245R: prevents DYRK1A autophosphorylation; > LoF mutations (e.g., E396ter: protein product degraded by ubiquitin proteasome pathway, inactive kinase, no dominant negative effect; other predicted LoF mutations: I48K(fs*2), A498P(fs*94), E414V(fs*76) (loss of exon 11, kinase domain mutation); > *in ovo* GoF in chick spinal cord: reduced proliferation; pharmacological LoF: increased proliferation and apoptosis; > embryonic overexpression upregulates p27Kip1 in the embryonic chick spinal cord and mouse cortex; > *in utero* GoF in mouse cortex: reduced proliferation, abnormal radial migration, enhanced neuronal differentiation, phenotypes dependent on timing and degree of over-expression; > Trisomy of *Dyrk1a* (in mBAC TgDyrk1a mice): lengthened G1 and RG cell cycle length, altered numbers of neurons and IPCs during embryonic neurogenesis; > *minibrain* (*Drosophila* ortholog): GoF promotes cell cycle exit, facilitates neuronal differentiation; haploinsufficiency results in microcephaly > *Dyrk1a* homozygous KO mice: growth delays, die at midgestation; *Dyrk1a* heterozygous +/- mice: reduced brain size, increased neuronal density; > cortex-specific *Dyrk1a* deletion: decreased cortical mass, reduced neuronal size, disrupted growth factor signaling; heterozygous mutants: changes in axonal projections and deeper layer neuron morphology; increased ASD-related behaviors; > *in vitro* knockdown: altered dendritic growth and spine development	***Select genetic studies:*** *De Rubeis et al., 2014; Iossifov et al. 2015; Bronicki et al., 2015; Ji et al., 2015; Dang et al., 2018; Moller, et al. 2008; van Bon et al., 2016; Courcet, et al. 2012; van Bon et al., 2011; Lee et al., 2020; Iossifov et al. 2015; Deciphering Developmental Disorders 2015; Iossifov et al., 2012; Ruaud et al., 2015* ***Select functional references:*** *Tejedor, 1995; Dang et al., 2018; Fotaki, et al. 2002; Lee et al., 2020; Yabut et al., 2010; Evers et al., 2017; Shaikh et al., 2016; Fotaki et al., 2004; Hammerle et al., 2011; Levy et al., 2021; reviewed by Park and Chung, 2013; Guimera et al., 1996; Najas et al., 2015; Chakrabarti et al., 2007; Kurabayashi and Sanada, 2013*
MEF2C	nonsense mutation, deletions	ASD, DD, mental retardation	encodes a calcium-dependent member of the MADS box family of TFs	> genome wide analyses for TF binding sites: MEF2 controls many activity-dependent genes > LoF mutations in hiPSC-derived cortical neurons: aberrant electrophysiological properties, including elevated synaptic activity and increased excitation; > conditional *Mef2c* deletion in developing interneurons: reduced PV+ cell density, deficits in PV cell maturation; > *Mef2c* cKO in excitatory lineage: attenuated cortical network activity and ASD-, ID- and schizophrenia-related behaviors; > *Gfap*-Cre mediated *Mef2c* KO: increased excitatory synapse numbers, upregulated synaptic transmission, impairments in learning and memory; > *Mef2c* cKO in NSPCs (*Nestin*-cre): abnormal cytoarchitecture/compaction of cells in CP, altered cortical organization; > Mef2c KO mice: immature electrophysiological properties, reduced excitability; > expression of superactivating MEF2C: decreased frequency of mEPSCs	***Select genetic studies:*** *Novara et al., 2010; Neale et al., 2012* ***Select functional references:*** *Mayer et al., 2018, Allaway et al., 2021; Harrington et al., 2016; Trudler et al., bioRxiv 2020; Li et al., 2008; Barbosa et al., 2008; Flavell et al., 2008*
RBFOX1	copy number variants	ASD, ID, epilepsy	encodes an RNA binding protein and activity-dependent splicing regulator	> encodes member of a family of splicing factors that regulate ion channels and synaptic proteins (e.g. *Cacna1c*); > 160kb deletion in first exon and intron: reduced expression of *Rbfox1* mRNAs; > knockdown: abnormal alternative splicing, abnormal neuroblast migration, impaired axon extension, impaired dendritic arborization, abnormal membrane and synaptic properties, increased neuronal excitability; > interneuron specific cKO: abnormal alternative splicing, increased PV- and SST-expressing interneuron density, impaired interneuron activity (i.e., decreased mIPSC frequency and amplitude, increased cFos expression), increased seizure susceptibility, altered synaptic connectivity; > CNS-specific knockdown: increased seizure susceptibility, increased neuronal excitability, and abnormal splicing	***Select genetic studies:*** *Hamada et al., 2016; Sebat et al., 2007; Martin et al., 2007; Bhalla et al., 2004; Mikhail et al., 2011; Davis et al., 2012; Zhao, 2013; Gandal et al., 2018; Davies et al., 2015* ***Select functional references:*** *Wamsley et al., 2018; Gehman et al., 2011; Martin et al., 2007; reviewed by Bill et al., 2013; Tang et al., 2009*
SRCAP	de novo LoF variants, truncating variants, frameshift variants, missense variants	ASD, FHS	encodes an activator of the calcium-sensitive transcriptional coactivator CREBBP	> FHS variants map to last two exons of SRCAP (33 and 34), DNA methylation profiles vary depending on the location of the mutation	***Select genetic studies:*** *Hood et al, 2012; Iossifov et al., 2014; Stessman et al., 2017; C Yuen et al., 2017; Rots et al., 2021; reviewed by Alonso-Gonzalez et al., 2018*

Footnote: Autism Spectrum Disorders (ASD); Benign Familial Neonatal Seizures (BFNS); Epileptic Encephalopathy (EE); Schizophrenia (SCZ); Intellectual Disability (ID); Developmental and Epileptic Encephalopathy (DEE); Childhood Absence Epilepsy (CAE); Developmental and Epileptic Encephalopathy (DEE); Developmental Delay (DD); Floating-Harbor syndrome (FHS); Timothy syndrome (TS); Bipolar Disorder (BPD); Episodic Ataxia Type 2 (EA2); Familial Hemiplegic Migraine (FHM); Generalized Epilepsy with Febrile Seizures Plus (GEFS+); Early-infantile EE Type 13 (EIEE13); Early Myoclonic Encephalopathy (EME)

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