Rare genetic brain disorders with overlapping neurological and psychiatric phenotypes.

Kathryn J Peall,[1,2] Michael J Owen,[1,2,3] Jeremy Hall[1,2]

[1]Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, UK

[2]Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ

[3]Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Hadyn Ellis Building, Maindy Road, Cardiff, CF24 4HQ

Corresponding Author

Kathryn Peall, Neuroscience and Mental Health Innovation Institute, Cardiff University, Cardiff, UK. Email: PeallKJ@cardiff.ac.uk

Word Count: 5976

Abstract

Understanding of rare, genetic brain disorders, spanning neurological and psychiatric phenotypes, is of increasing importance given their potential for disease model development, and implications for more common, polygenic forms. However, the traditional clinical boundaries of neurology and psychiatry result in frequent segregation of these disorders into distinct silos, limiting cross-specialty understanding to facilitate clinical and biological advancement. This perspective piece highlights multiple genetic brain disorders in which neurological and psychiatric phenotypes are observed, but where in depth, cross-spectrum clinical phenotyping is rarely undertaken. We describe the combined phenotype observed in genetic disorders linked with epilepsy, dystonia, autism spectrum disorder and schizophrenia, identifying common underlying mechanisms centring on synaptic plasticity, including changes to synaptic and neuronal structure, calcium handling and balance of excitatory-inhibitory activity. Further work is needed to better define and replicate these phenotypes in larger cohorts, gaining greater understanding of pathophysiological mechanisms and potential for identification of common therapeutic targets.

Introduction

Rare, genetic brain disorders are often classified as "neurological" or "psychiatric" with clinical services and research groups similarly polarised. However, in many instances those with "neurological" diagnoses have psychiatric signs and symptoms, and vice versa. In addition, increasing evidence suggests shared underlying pathophysiological mechanisms, namely impaired neuronal functional performance disrupting the balance of excitatory/inhibitory neuronal activity.[1] For example, such disorders may present to clinical services with epilepsy (*SCN1A*, *CACNA1A*, *PCDH19*, *KCNQ2*, *GRIN2A*), dystonia (*SGCE*, *TOR1A*, *GNAL*, *KMT2B*), autism (*FMR1*, *SHANK3*, *CHD8*, *MECP2*, *CACNA1C*) or schizophrenia (*SETD1A*, *CACNA1G*, *TRIO*, *GR1A3*) but be associated with a range of other neurological and psychiatric phenotypes.[2,3] In addition, research studies, notably during the gene discovery phase, focus recruitment based on the presence or absence of a specific set of diagnostic signs or symptoms, with only limited phenotypic evaluation at this stage, frequently leading to genes being labelled as 'disease-specific'.

While multiple pathological copy number variants (CNVs) such as 22q11.2 and 16p11.2 deletion syndromes, have been linked with neurodevelopmental phenotypes spanning neurological and psychiatric symptoms, these are beyond the scope of this review and have been discussed in detail elsewhere.[4-6] Additionally, previous studies have examined the degree of genetic overlap between neurological and psychiatric disorders using genome-wide common variant risk, identifying a high degree of genetic correlation across psychiatric disorders, but not for neurological disorders, or between neurological and psychiatric disorders. However, this included a broad group of both degenerative and non-degenerative neurological diagnoses (e.g. Alzheimer's disease, intracerebral haemorrhage and ischaemic stroke), and without the focus on those where psychiatric symptoms are considered to form a central component of the disorder phenotype.[7]

By contrast, this perspective piece will focus on highly penetrant single gene variants identified as being causative in disorders where there is evidence, albeit limited in places, for both neurological and psychiatric phenotypes, and where model systems can more easily facilitate investigation of clinical phenotype and underlying biological mechanisms. We do not provide exhaustive coverage of these disorders but have sought to provide examples from four main clinical diagnoses – epilepsy, dystonia, autism spectrum disorder (ASD) and schizophrenia – considering these brain disorders from their genetic perspective, evaluating the phenotypic evidence across clinical boundaries, the approaches taken to clinical assessment, and subsequent review of potential common underlying biological mechanisms at synaptic, neuronal, and intracellular level.

Genetic Neurological Disorders

Epilepsy

Case reports and clinical observation have long indicated the co-morbidity of psychiatric phenotypes in adults epilepsy with an estimated prevalence of 23.1%, 20.2% and 15.2% for depression, anxiety and ASD respectively, across epilepsy cohorts.[8-10] Similar outcomes have been observed in studies focused on children and adolescents diagnosed with epilepsy, despite the relatively larger burden of neurodevelopmental disorders. Here, population levels studies have estimated a 43% prevalence of co-morbid psychiatric symptomatology with odds rations of 10.7, 5.4, 2.3 and 1.8 for ASD, attention deficit hyperactivity disorder (ADHD), anxiety and depression respectively.[11] Prospective phenotypic data capture however, suggests a bidirectional relationship between ictal activity and psychiatric diagnoses with a more recent UK study identifying that those diagnosed with depression carried a 2.5-fold increased risk of developing epilepsy and prior to seizure onset, risk of suicide is 2.9-fold higher than that observed in the general population.[12,13] Population-level genetic meta-analyses also indicate significant associations between major depressive disorder (MDD) and attention deficit hyperactivity disorder (ADHD) with epilepsy ($p=0.001$ and $p=0.020$ respectively), with MDD noted to increase the risk of focal epilepsy, while a higher risk of generalised epilepsy was observed in those diagnosed with ADHD.[14] A summary of key epilepsy related genes, their associated function, and neurological and psychiatric symptoms is available in Table 1, with those where more evidence exists for overlapping phenotypes discussed in further detail below.

SCN1A

Variants in *SCN1A* are associated with a spectrum of epilepsy syndromes, ranging from genetic epilepsy with febrile seizures (GEFS+) to treatment resistant epileptic encephalopathies, the most common of which is Dravet syndrome. Dravet syndrome phenotype not only involves intractable seizures but also delayed psychomotor development, intellectual deficits, and behavioural difficulties, the latter including attention deficit, hyperactivity, mood instability, perseveration, and impulsivity.[15-18] Cross-sectional studies report autistic traits to be present at rates between 8.3% and 61% dependent on the methods of assessment, with the most commonly described features including delayed speech (91.9%), restricted interests and obsessions (24-69%), adherence to routine, repetitive behaviours, lack of emotional reciprocity and language regression (10.8%).[19-21] Interestingly, the reported rates of ASD are lower in children (24-40%) compared to equivalent studies in adults, where rates as high as 61.5% have been found.[14] Moreover, genetic analysis of ASD cohorts have also identified pathogenic variants in *SCN1A*, providing further support for overlapping mechanisms across these phenotypes.[22] Interestingly, the accuracy of distinct genetic testing approaches in identifying *SCN1A* mutations has found, as with many genes, that both Sanger sequencing and next generation sequencing approaches (whole exome and whole genome sequencing) carry limitations. As such, if an initial approach yields the absence of a pathological *SCN1A* variant, yet the

clinical phenotype is consistent with the disorder, the alternative form of genetic testing should be considered.[23]

PCDH19

Pathogenic *PCDH19* variants typically result in seizure onset at ~9 months of age, with females affected in 95% of cases and affected males typically demonstrating mosaicism.[24] Varying degrees of developmental delay and cognitive impairment are observed in all mutation carriers however, the predominant psychiatric features include ASD, ADHD, Obsessive-Compulsive Disorder (OCD), anxiety, and psychotic disorders including schizophrenia, with evidence that earlier age at epilepsy onset is associated with a higher risk of ASD and intellectual disability.[25] A cross-sectional online survey of 112 *PCDH19* mutation carriers found 60% of the cohort to exhibit features of ASD, often coupled with co-morbid symptoms of ADHD. Twenty-one percent met clinical diagnostic criteria for OCD, with no observed overlap with those experiencing ASD symptoms, with those diagnosed with ASD tending towards having a higher number of seizures.[26] In a separate study of 60 female *PCDH19* mutation carriers, all diagnosed with epilepsy, 21% were reported to have developed some form of psychotic disorder, including schizophrenia, schizoaffective disorder or unspecified psychotic disorder, with median age at onset of 21 years (11-28 years), considered to be a later onset feature in the context of the *PCDH19* phenotype. Further evaluation of this group found no link between psychotic symptoms and intellectual impairment.[27]

KCNQ2

KCNQ2 pathological loss of function variants give rise to a clinical phenotype extending from self-limiting familial neonatal epilepsy to developmental and epileptic encephalopathy where seizures present in the first weeks of like, but resolve over subsequent years with some degree of residual developmental impairment.[28] However, evidence for genotype-phenotype correlation remains limited with variable clinical evolution associated with recurrent pathological variants. ASD is a recognised co-morbid psychiatric feature with those affected demonstrating traits such as repetitive movements, poor eye contact, self-harm, and social impairment, features mirrored in heterozygous loss-of-function *KCNQ2* murine models. [29-32] Interestingly, rarer heterozygous gain-of-function *KCNQ2* missense variants have more recently been identified where a distinct neurological phenotype is observed extending from non-epileptic myoclonus and marked intellectual impairment to milder forms involving epileptic spasms and developmental delay however, autism remains the most prominent psychiatric feature (67%) with 40% also meeting diagnostic criteria for ADHD.[33]

GRIN2A

Pathological variants in *GRIN2A* have been linked with a spectrum of neurodevelopmental disorders, typically with pronounced speech-related impairment and epilepsy.[34] Case reports have described autistic features, including repetitive actions, poor initiation of social interaction, and cognitive rigidity, alongside the seizures[35,36] A cross-sectional study (n=248) of individuals with pathogenic or likely pathogenic *GRIN2A* variants identified a broad range of characteristics from normal or near-normal development with mild epilepsy and speech delay/apraxia, to severe developmental and epileptic encephalopathy, coupled with hypotonia (28.8%) and movement disorders (26.4%) including ataxia, dystonia, chorea and spasticity.[37] Similar clinical features were observed in another study of 18 participants with 12 unique missense variants with reported phenotypes including seizures (50%), intellectual disability (100%), hypotonia (61%) and autism (11%).[38] More recently rare, highly penetrant variants have been reported In schizophrenia and ASD cohorts, suggesting a potential role in these disorders.[37,39-42] One such study, albeit involving a relatively small cohort, examining both schizophrenia (n=429) and ASD (n=428), focused on rare pathogenic variants in the NMDAR, sequencing each of the seven genes encoding the multiple receptor subunits. Two *de novo* *GRIN2A* pathogenic variants were identified within the schizophrenia cohort and a single *de novo GRIN2B* mutation in a patient with ASD.[42-44]

CACNA1A

Pathogenic *CACNA1A* variants result in multiple neurological phenotypes, for example episodic ataxia type 2 (EA2) and familial hemiplegic migraine (FHM). Within these disorders a proportion of patients also develop seizures, often in conjunction with cerebellar dysfunction and early neurodevelopmental impairment.[45] The nature of the seizures varies dependent on the underlying disorder such that in those with EA2 the seizures typically present pre-ataxia, while with FHM seizures most typically occur in conjunction with a hemiplegic attack.[46] Reported co-morbid neuropsychiatric features include ADHD and impulsivity (69%), intellectual disability (38%), and ASD (25%).[47]

Dystonia

As with many movement disorders, non-motor symptoms, and most notably psychiatric symptoms, are of increasing interest and importance in understanding the dystonia phenotype.[48] This, in part, has evolved from dystonia being considered a functional or psychiatric disorder until the late 1970s, with support for its consideration as a movement disorder following identification of the first disease causing gene (*TOR1A*, DYT1) twenty years later.[49] However, there also exists an ongoing debate as to whether co-morbid psychiatric symptoms represent a primary or secondary components of the dystonia phenotype, particularly in the context of a visible, stigmatising motor disorder. However, population level, longitudinal, linked clinical data studies provide an opportunity, not dependent upon the recall bias of individual patients, to evaluate the temporal pattern of psychiatric disorder diagnosis relative to motor disorder

diagnosis. These have demonstrated in specific adult-onset idiopathic forms that psychiatric diagnoses, predominantly depressive and anxiety-related disorders, precede onset of the motor symptoms by several years, and rather than increasing post-motor diagnosis, stabilise or gradually decrease with time, suggesting their role as a core phenotypic component.[50,51] Another study applied an unbiased systems-biology approach to investigate the cellular specificity of known dystonia causing genes, predict their functional relationships and test whether dystonia and neuropsychiatric disorders share a genetic relationship. Here, significant enrichment was observed for the heritability of MDD, OCD and schizophrenia within the putamen, frontal cortex, and white matter modules, further supporting a biological link between dystonia and psychiatric disorders[2] A summary of dystonia genes, their function and key clinical phenotypes are outlined in Table 1.

SGCE

Myoclonus Dystonia, caused by mutations in the maternally imprinted *SGCE* gene, represents the genetic form of dystonia in which most of the psychiatric phenotyping has been undertaken. This evolved from initial case reports highlighting an excess of a broad range of psychiatric symptoms including depression, OCD, substance abuse, anxiety, phobic and psychotic disorders,[52,53] with substance abuse focused on alcohol excess likely due to its effect in suppressing the motor features. An Initial meta-analysis of previous studies suggested that pathogenic *SGCE* variants themselves may contribute to excess alcohol intake however, prospective work comparing *SGCE*-mutation positive and alcohol responsive tremor cohorts failed to replicate these findings.[54,55] Subsequent case-control studies have refined the psychiatric phenotype to include generalised anxiety disorder, specifically social anxiety and panic disorder, together with OCD, in which excess compulsivity and not obsessionality was observed.[55-57]

TOR1A

The first identified Mendelian inherited dystonia gene is associated with a motor phenotype of childhood onset generalised dystonia, with several initial studies examining for evidence of a psychiatric phenotype based on anecdotal clinical experience. Case-control comparison of 96 motor affected *TOR1A* GAG deletion carriers were compared to 60 non-motor manifesting mutation carriers, and 65 non-carriers. This study found an increase in the relative risk of depression across all mutation carriers, both with and without motor symptoms, compared to unaffected family members. *TOR1A* mutation carriers were also found to have an earlier age at onset of depressive symptoms, the severity of which was unrelated to motor symptom severity, with additional work finding no evidence of higher rates of OCD.[58,59] However, a more recent study aimed at exploring the potential shared genetic pathogenesis of ASD and OCD identified eight potential common risk genes across the two disorders with *TOR1A* being one of those identified.[60]

GCH1

Autosomal dominantly inherited *GCH1* mutations result in one of several forms of dopa-responsive dystonia, in which disfunction of key enzymes within the dopamine metabolic pathway have been identified. Given the involvement of dopamine, a neurotransmitter historically implicated in multiple neuropsychiatric disorders, several studies have examined the psychiatric phenotype within this patient group.[61] The most consistent finding is that of a higher rate of affective disorders, primarily depression, with ~50% of larger cohorts reported to have experienced at least one episode of MDD, and 31% of this group experiencing recurrent symptoms.[62] In addition, while the onset of motor symptoms is almost exclusively in childhood, where psychiatric symptoms have emerged, these have tended to develop in adult life, potentially indicating modification of the psychiatric symptoms by neurodevelopment, or a secondary phenotypic contribution.[63]

GNAL

Pathogenic GNAL variants have recently been identified, predominantly in adult-onset forms of dystonia.[64] Early linkage studies implied that GNAL variants were linked to both schizophrenia and bipolar disorder, although this has not been borne out in subsequent genome wide association studies (GWAS) or next generation sequencing (NGS) approaches.[65] However, a study using a genome-wide CNV approach with samples from individuals diagnosed with ASD, ADHD, schizophrenia and OCD, identified rare CNVs (defined as <0.1% in control samples) in 284 (10.5%) of the total cohort, with *GNAL* being one of eleven neurodevelopment-associated genes linked to >1 of the neuropsychiatric disorders listed above, with these being ASD and ADHD in the context of *GNAL*.[66]

Genetic Psychiatric Disorders

Much of the research to date relating to highly penetrant rare variants in psychiatric disorders has focused on neurodevelopmental disorders, with these representing a clinically heterogenous group spanning varying levels of intellectual impairment, autistic traits, ADHD, psychotic symptoms and dysmorphisms.[67] While there is some inevitable degree of overlap, we have instead attempted to focus on those genes linked more specifically with psychiatric disorders where there is additional evidence of a neurological phenotype (Table 2).

<u>Autism Spectrum Disorder</u>

The estimated prevalence of ASD is 1 in 54 individuals at a population level, with an estimated 25% experiencing co-morbid neurological symptoms, often involving motor impairment, epilepsy and sleep disorders.[68] Motor dysfunction in ASD has long been recognised with key literature dating back 40 years suggesting a role for the mesolimbic cortex and fronto-striatal circuits in contributing to motor disturbance

in ASD.[69] Despite only repetitive behaviours being included in the ASD diagnostic criteria, multiple other motor deficits are recognised including persistent gross and fine motor impairment, motor developmental delay, and difficulties with praxis, gait and co-ordination.[70,71] The first reports of seizures in ASD date back to the early 1940s, with prevalence now estimated at 30% in ASD cohorts and a bimodal distribution of seizure onset in early childhood and adolescence.[68,72,73] Within ASD cohorts there has also been an observed association between intellectual disability and epilepsy, while rates of ASD in children diagnosed with epilepsy placed at ~46%.[74,75] Although heritability in autism has been recognised for several years, most frequently linked with common genetic variants,[76,77] more recent evidence suggests that highly penetrant, rare genetic variants as causative in a subset of these individuals diagnosed with ASD.[78]

FMR1

Pathogenic trinucleotide (CGG) expansion within the *FMR1* gene can give rise to multiple clinical phenotypes dependent on the number of repeats, including Fragile X syndrome (FXS) (>200 CGG repeats) and Fragile-X-Associated Tremor/Ataxia syndrome (FXTAS) and Fragile X-Associated Primary Ovarian Insufficiency (FXPOI) (55-200 CGG repeats). The CGG expansion results in methylation and silencing of the FMR1 gene, causing loss of expression of the Fragile X Mental Retardation 1 Protein (FMRP), leading to multiple symptoms including intellectual disability, ASD, social anxiety, speech and language delay.[79] Diagnoses of autistic traits or ASD are most common in the FXS form, together with hyperactivity, anxiety and difficulty with social interaction. However, there is also an increased seizure risk during the first 10-years of life, with ASD evident at a significantly higher rate in those with seizures compared to those without.[80] FXTAS, by contrast, is typically characterised as a motor syndrome of late-onset, progressive cerebellar ataxia and intention tremor. Higher levels of psychiatric co-morbidity are also recognised amongst affected males with elevated rates of ADHD (93% vs.13%) and ASD (79% vs.0%) compared to matched unaffected individuals.[81,82] Higher rates of psychiatric symptoms, compared to unaffected controls, are also seen amongst non-motor manifesting FXTAS premutation carriers, including obsessive-compulsive symptoms in men, and somatisation and depression in women.[83] Finally, in those with an adult-onset FXTAS motor phenotype evidence suggests a 65% lifetime prevalence of mood disorders and 52% anxiety disorders (notably panic disorder and specific phobia), with onset of the mood symptoms frequently pre-dating development of motor and cognitive impairment.[84]

SHANK3

CNVs and chromosomal rearrangements involving chromosome 22 have been recognised for several decades, with early description of the ring chromosome 22 phenotype including autistic behaviours, impaired motor function, dysmorphic features and global developmental delay.[85] As the resolution of genetic screening techniques have evolved, these phenotypes have been mapped to the *SHANK3* gene,[86,87]

recognised as the strongest candidate gene within the 22q13.3 microdeletion syndrome region to contribute to the neurobehavioural symptoms and wider clinical observed.[88] Given this long association with ASD,[88] a more recent meta-analysis of *SHANK3* point mutations and CNVs sought to determine their overall prevalence and clinical importance across ASDs.[89] Overall, all mutation types in all three *SHANK (SHANK1, 2,* and *3)* genes were present in ~1% of individuals diagnosed with ASD where *SHANK3* mutations were the most common (0.69%), present in >1 in 50 individuals with ASD and intellectual disability. Systematic clinical evaluation of 77 individuals with pathogenic or likely pathogenic *SHANK3* variants, including CNVs referred to as Phelan-McDermid syndrome, identified evidence of intellectual disability in all 77 cases, while 73% also had symptoms consistent with ASD. Motor neurological examination found significantly better gross motor skill performance compared to fine motor function (p=0.002), with hypotonia (16/17, 94%) and gait abnormalities (toe walking, gait apraxia and slow walking) (14/17, 82%) present in almost all cases. Seizures were also reported in five cases (29%), with pathological EEG abnormalities identified in a further five.[90] Pathogenic *SHANK3* variants have also been identified in two families from a cohort of 185 individuals diagnosed with schizophrenia, with the reported clinical phenotype also being broader and including intellectual difficulties, seizures, speech impairment and atypical psychosis.[91] More recently, an alternative approach, namely participant recruitment based on known 22q13.33 deletion or SHANK3 pathogenic variants, reinforced not only the wider clinical context associated with these genotypes, but also provided further additions, including mood disturbance, catatonia, urinary and gastrointestinal symptoms.[92]

CHD8

Loss-of-function variants in the chromodomain helicase DNA-binding protein 8 (*CHD8*) gene were initially described as being a risk factor for ASD but are increasingly associated with a wider spectrum of neurodevelopmental impairment including intellectual development disorder with autism and macrocephaly (IDDAM), and overgrowth and intellectual disability (OGID) syndromes. Clinical phenotyping of a cohort diagnosed with IDDAM (n=106) identified intellectual disability (68%), hypotonia (29%), behavioural abnormalities (88%) including ASD (76%), short attention span (32%), abnormal social behaviour (31%), sleep disturbance (29%) and impaired social interactions (28%).[93] Analysis of a further 25 individuals with CHD8 protein truncating variants found an increased prevalence of traits including ASD (84%), intellectual disability (81%), speech regression (37%), seizures (27%) and hypotonia (27%) amongst affected males.[94] More recently, whole exome sequencing identified likely pathogenic *CHD8* variants (nonsense and frameshift) in two unrelated patients with overlapping phenotypes involving generalised dystonia and mild-to-moderate neurodevelopmental impairment. Both had undergone deep brain stimulation (DBS) for treatment of the dystonia, with improvement to motor function, suggesting an additional role in motor phenotypes such as dystonia.[95]

CACNA1C

Gain of function mutations in *CACNA1C* are most commonly associated with Timothy syndrome (MIM 601005), a multisystem channelopathy with prominent cardiac defects, craniofacial abnormalities, intellectual disability, ASD, hypotonia and epilepsy.[96] However, more recently *CACNA1C* variants have been linked with a more prominent neuropsychiatric phenotype, albeit through small effect SNP alleles, including increased risk of schizophrenia, MDD, bipolar disorder, and ASD, while in a single kindred a heterozygous intronic variant segregated with an adult-onset autosomal dominant cerebellar ataxia phenotype.[97-99] More recently, 25 individuals from 22 families with novel *CACNA1C* variants were reported as all exhibiting a neuropsychiatric phenotype including developmental delay, intellectual disability, ASD, hypotonia, childhood-onset epilepsy, ataxia, in the absence of any observed cardiac defects or features more consistent with Timothy syndrome.[100] More specific evaluation of the neuropsychiatric features in 24 individuals harbouring pathogenic *CACNA1C* variants, both with and without cardiac involvement, identified developmental delay (92%), incoordination (71%), hypotonia (67%), ASD (50%), seizures (37.5%) and ADHD (21%).[101]

MECP2

MECP2 mutations give rise to Rett Syndrome with pathogenic variants most commonly arising *de novo* in paternal germline cells leading to almost exclusively female inheritance, although males with *MECP2* mutations tend to be more severely affected with more rapid symptom progression.[102,103] The diagnostic features of Rett Syndrome include loss of expressive language skills, deterioration in upper limb fine motor skills, reduction in mobility and the development of stereotypic movements of the hands. The typical natural history is of initial normal development followed by head growth deceleration, global cognitive decline, and motor developmental delay, usually between 1.5 and 3 years of age, with variable residual language and hand function skills.[104] Autistic traits consistent with the diagnostic criteria for ASD are evident in a subset of individuals (20-50%), predominantly during the regression period, with persistent deficits in social communication and interaction skills in 10-15% of female patients.[105,106] Several studies have found deterioration in motor and functional skills in later adult life, with reports of the development of parkinsonian features.[107,108]

Schizophrenia

While the overall prevalence of schizophrenia is ~1% within the population with genetic aetiology in the majority being focused on multiple low penetrance, common genetic variants and their overall contribution to a polygenic risk score, more recent work has indicated that rare, highly penetrant pathogenic variants are also likely to contribute to this diagnostic group.[39,109,110] These rare variants have also been found to be

prioritised in common variant analyses suggesting potential biological commonality across the spectrum of genetic aetiology in schizophrenia, with development of rare variant model systems potentially providing pathophysiological insights applicable to the wider context of schizophrenia. Investigation of these rare variants has found a wider phenotypic spectrum beyond schizophrenia, including intellectual disability, ASD, and epilepsy, reflecting a longstanding recognition of a broader clinical phenotype, including more typically considered neurological traits, often referred to as 'Neurological Soft Signs' in schizophrenia. Cognition and motor function are often included within the spectrum of these soft signs, with these including impairments to motor co-ordination and ability to perform complex motor tasks These soft signs are recognised in the majority of those diagnosed with schizophrenia, including both those naïve to neuroleptic treatment and those with chronic symptoms. There is also evidence that the neurological signs can precede the onset of psychosis and can be used to identify those individuals at risk of a more unfavourable, chronic clinical symptom course.[111-113]

SETD1A

Several earlier studies identified *de novo* loss of function *SETD1A* variants as conferring high risk of schizophrenia, with more recent work extending the phenotype to include developmental delay, intellectual disability and epilepsy.[114-116] Longitudinal work has suggested a varying natural history of phenotype, dependent on mutation type, with loss-of-function variants leading to an early neurodevelopmental syndrome, with a proportion developing schizophrenia later in life.[117] Studies focused on younger individuals (34 months-23 years) have described clinical phenotypes to include behavioural difficulties, including aggression, anxiety, autistic behaviour, and neurological abnormalities involving motor developmental delay, hypotonia and seizures.[115] More specific focus on psychotic disorders within this group identified no formal diagnoses but described relevant psychopathology in two individuals; a 23-year old male with alternating periods of euphoria and negative symptoms, such as social withdrawal, and a 16-year old female with reports of a previous transient episode of visual and auditory hallucinations.[115] However, onset of schizophrenia typically presents in the early 20s, and therefore longer term follow-up of this cohort may reveal a wider prevalence of psychopathology.

GRIA3

Pathogenic *GRIA3* variants have been linked not only with schizophrenia and bipolar disorder,[118] but more recently a wider phenotype involving intellectual disability, dysmorphic features, disturbed sleep and epilepsy.[119-121] While there remains a lack of larger cohort studies with in depth clinical phenotyping, case reports and case series continue to widen the clinical phenotype spanning neurological and psychiatric features including hypotonia, motor developmental delay, hyporeflexia, language delay, exaggerated startle reflex, generalised chorea, and multifocal myoclonus.[122,123]

TRIO

Use of next generation sequencing approaches across several studies have identified rare *TRIO* variants in those with more general neurodevelopmental phenotypes such as intellectual disability, schizophrenia, ASD, speech apraxia and epilepsy.[124-127] However, more recent work has focused on *TRIO*-specific cohorts with consistently reported phenotypes including global developmental delay, intellectual impairment, seizures, tremor, ataxia and speech disturbance.[128-130]

Summary of overlapping phenotypes

A summary of the overlapping clinical phenotypes described above are outlined in Figure 1, with several patterns beginning to emerge. Genes linked with seizures are almost exclusively observed to exhibit symptoms consistent with ASD (*SCN1A* and *SYNGAP1*), or ASD and ADHD (*KCNQ2*, *GRIN2A*, *CACNA1A*), while those harbouring *PCDH19* have been reported to develop seizures, ASD, and schizophrenia. Genes linked with ASD are equally divided between those with overlapping motor phenotypes (*FMR1*, *FOXP1*, *CHD8*) and those with both impaired motor function and seizure activity (*SHANK3*, *MECP2*, *CACNA1C*). Similarly, several dystonia causing genes (*GNAL*, *KMT2B*) also have overlapping motor/ASD phenotypes, while the majority of the remaining dystonia genes discussed manifest either anxiety-related symptoms (*SGCE*, *KMT2B*, *GCH1*) or depression (*TOR1A*, *GCH1*, *KMT2B*). Finally, genes linked with schizophrenia appear to consistently involve more complex phenotypes, for example *SETD1A* and *TRIO* demonstrating evidence of schizophrenia, seizures, and motor impairment, while schizophrenia, seizures, ASD have been reported in those harbouring pathogenic *GRIA3* variants. The emerging picture suggests that although links with neurodevelopment are more widely acknowledged with neuropsychiatric disorders, single genes involved in neurological disorders also appear to frequently impact, and play a role, in development. However, a common theme across these rare, genetic brain disorders is that few studies have sought to systematically assess both “neurological” and “psychiatric” symptoms and that significant further work is required, not only to verify these links but also to develop a wider, more comprehensive understanding of the true clinical picture associated with each of these genes.

Common neuronal and cellular mechanisms

Single gene disorders provide an opportunity for the development of model systems in which to examine underlying pathophysiological mechanisms. Development of genetic models where the clinical phenotype spans overlapping neuropsychiatric symptoms provide opportunity to identify common mechanistic underpinning, gain insight as to why these phenotypes may co-exist, and potential identification of effective therapeutic targets. An area of consistent interest across both neurological and psychiatric fields has been that of synaptic plasticity, and how changes at a synaptic level may impact functional neuronal and network

level activity. Several large scale genetic analyses provide further support for the importance of synaptic plasticity, with one of those focusing on loss-of-function variants in ASD where the majority of the genes involved were encoded synapse related proteins, including voltage-gated ion channels regulating action-potential generation, neuronal pace-making, and excitability-genetic transcription coupling.[131] Below, we focus on three potentially key mechanisms; synaptic structure, dendritic arborisation, and calcium signalling, and how these may contribute to disrupted functional activity, and in particular the balance of neuronal excitatory-inhibitory (E-I) activity (Figure 2).

Synaptic structure

Multiple disease-related models indicate that disruption to synaptic structure, with subsequent impact on function and plasticity, is a key pathophysiological mechanism in multiple genetic brain disorders, most notably at excitatory glutamatergic synapses (Figure 2A).[132,133] Within the context of the genes discussed above, several have been implicated at both pre- and post-synaptic terminals. Pre-synaptically, the Syntaxin 1B protein, encoded by *STX1B*, forms a core component of the N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex involved in the exocytosis of synaptic vesicles into the pre-synaptic space. Multiple model systems have shown pathogenic variants to results in loss of neurotransmitter release, inhibition of pre-synaptic vesicle priming and disruption of versicle docking at both glutamatergic and GABAergic synapses.[134-136] Trans-synaptic adhesion molecules, namely pre-synaptic neurexin and post-synaptic neuroligins, have been implicated in multiple of these genetic disorders, with Neuroligin-4, itself also directly implicated in autism.[137] Included within these genes is *TRIO*, a Rho guanine nucleotide exchange factor (RhoGEF), involved in glutamatergic synapse formation, in part through its interaction with Neuroligin-1. Pathogenic variants, particularly within the GEF domain of the protein, appear to disrupt this interaction, impairing synapse formation as well as impacting NMDAR function.[138] Rodent models have shown *Shank3* to bind the cytoplasmic tail of neuroligin, inducing both pre- and post-synaptic changes via the Neurexin-Neuroligin transsynaptic scaffold, which in turn regulates AMPA and NMDA-receptor mediated transmission, all of which become impaired in the presence of pathogenic variants.[139] Finally, *SGCE*-mutation positive iPSC models were also shown to disrupt the balance of this adhesion molecule complex with higher pre-synaptic neurexin-1 and lower post-synaptic neuroligin-4 levels, potentially linked with their additionally observed increased functional neuronal activity, compared to controls.[133] On the post-synaptic membrane, G*RIN2A,* encodes an isoform of the GluN2 subunit of NMDARs which binds glutamate causing neuronal depolarisation, raised intracellular Ca^{2+} levels and subsequent modulation of synaptic strength.[140] Transgenic *GRIN2A* murine models demonstrate enhanced efficacy of glutamate at the NMDAR, slower receptor deactivation following glutamate removal, as well as changes to the CaMKIIα phosphorylation pathway causing decreased NMDAR trafficking, all coupled with increased neuronal excitability.[141,142] *SHANK3* also forms part of the NMDAR post-synaptic scaffold structure (PSD95-

GKAP-Shank3-Homer), linking it to metabotropic mGlu5 receptors and in so doing regulating NMDAR function. Disruption to this physical structure blocks NMDAR activity, in turn disrupting neuronal function and plasticity.[143]

Dendritic structure and arborisation

Dendritic branching patterns both impact and are influenced by neuronal functional activity, with multiple model systems for the genes discussed in this review demonstrating impact on axonal growth and dendritic arbor (Figure 2B).[144,145] Pathological *SYNGAP1*, *SETD1A*, *TRIO*, *SGCE* and *FMR1* variants are all linked with more complex dendritic morphology, predominantly involving cortical glutamatergic neurons, with murine and human iPSC loss-of-function *SYNGAP1*, *SETD1A* and *SGCE* models resulting in larger dendritic spines, more complex morphology, and a higher number of excitatory synapses with greater functional activity.[133,146,147] The reduction in FRMP levels associated with FXS have also been linked with increases in spine density, with the spines themselves appearing longer and thinner,[148] an effect reversed with the application of mGluR5 antagonist.[149-151]A similar morphological phenotype with pathological *TRIO* variants has been observed in hippocampal neurons, impacting early neuronal network formation through increased neurite outgrowth and a higher number of functional synapses.[127]

By contrast *FOXP1*, *CHD8*, *SHANK3* and *TOR1A* models have demonstrated a truncation in dendritic morphology with subsequent reduction in overall functional neuronal activity. Pathogenic murine *Foxp1* variants have been found to affect layer V cortical neurons with shorter dendrites and fewer branches, as well as disruption to neuronal migration and therefore laminar formation,[152] with similar features observed with RNAi knockdown of *CHD8* expression.[153] Given its role as a synaptic scaffold protein, morphological changes in the context of pathological *SHANK3* variants would be anticipated with neuronal models demonstrating impact in both early (fewer dendritic spines and reduced synaptic transmission) and later development (reduced neuronal soma size, growth cone area, neurite length and branch numbers).[154,155] Finally, there has been increasing evidence to support a role for the cerebellum in dystonia pathogenesis, supported by findings from murine *Dyt1* ΔGAG knock-in where both shorter primary dendrites and fewer spines on distal dendrites have been observed in cerebellar Purkinje cells.[156]

Calcium Signalling and intracellular homeostasis

Several genes discussed have been linked with changes to calcium handling, either directly via pathogenic variants in genes encoding calcium channels, or indirectly via intracellular and extracellular mechanisms (Figure 2C). Three calcium channel genes have been highlighted here; *CACNA1A*, *CACNA1C and CACNA1G. CACNA1A* encodes an alpha-subunit of the voltage-dependent P/Q-type calcium channel located in the neuronal cell membrane and is involved in fast synaptic transmission, neuronal excitability and

neurotransmitter release.[157,158,159] Murine null *Cacna1a* models demonstrate an increased T-type calcium current in the thalamocortical network, with overexpression inducing increased neuronal, and subsequent, ictal activity.[160,161] *CACNA1C* encodes the L-type Cav1.2 calcium channel (LTCC) involved in facilitating cellular calcium influx, initiating downstream signalling cascades including Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) leading to cAMP response element-binding protein (CREB) phosphorylation and gene regulation. Animal models have shown that LTCC antagonism reduces CREB-mediated long-term potentiation (LTP), and Cav1.2 knockdown reduces CREB-mediated transcription and LTP, demonstrating its role in gene expression and synaptic plasticity.[162-164]

Other genes linked with epilepsy and autism are indirectly linked with calcium handling, including the postsynaptic scaffold protein SHANK3. Here, murine *in vivo* studies of prefrontal cortical circuitry found *Shank3* mutations to be associated with higher calcium transients in apical dendritic spines, reducing NMDAR currents due to loss of dendritic inhibition, and reduced firing of inhibitory GABAergic interneurons.[165] Changes to calcium handling have also been implicated in several dystonia genes with *ANO3* encoding a Ca^{2+}-gated chloride channel, highly expressed in the striatum, with patient-derived cellular functional studies demonstrating abnormalities in endoplasmic-reticulum-dependent Ca2+ signalling.[166] At a network-level, patient-derived *SGCE* mutation iPSC lines, differentiated towards both excitatory glutamatergic and striatal medium spiny neuronal lineages demonstrate elevated levels of basal calcium levels but fewer calcium transients and longer interspike intervals, compared to controls, with changes in intracellular calcium handling believed to underpin these changes.[133,167] Finally, *PCDH19* encodes a membrane calcium-dependent cell-cell adhesion glycoprotein, a key contributor in cell adhesion during cortical development, with lower levels of spontaneous calcium influx, lower basal levels and lower maximal intracellular Ca^{2+} ions peaks observed in the context of pathogenic variants compared to wild-type controls[168,169]

Balance of excitatory/inhibitory neuronal activity

The frequent impact of the mechanisms outlined above is disruption to the balance of excitatory-inhibitory (E-I) neuronal activity, typically with overall increased excitation either directly through increased excitation, or indirectly via reduced inhibition, within these networks (Figure 2).[170] Higher levels of excitatory activity, predominantly in glutamatergic neurons, has been demonstrated in models systems across *KCNQ2*, *FXS* and *SGCE* variants. Conditional ablation of *Kcnq2,* encoding the Kv7 voltage-gated potassium channel, in layer 2/3 cortical pyramidal neurons of murine models results in neuronal hyperexcitability, increased action potential frequency and amplitude.[171-173] FXS is associated with increased signalling via metabotropic glutamate receptors and reduced inhibitory GABAergic synaptic signalling, producing an overall increase in excitatory activity,[170,174] and in *Sgce* mutant mice, high frequency stimulation at corticostriatal glutamatergic

synapses leads to loss of LTD, restored through application of adenosine 2A receptors ($A_{2A}R$) antagonists.[175] Within the basal ganglia *TOR1A* dystonia murine models demonstrate increased inhibitory striatal cholinergic interneuron tone, reversing the direction of D2R regulation of cholinergic intraneuronal activity, and increasing overall excitation.[176] Another similar *Tor1a* model also demonstrates early changes to cortico-striatal activity with premature LTP and an absence of LTD, resulting in an overall elevation of excitatory activity[177]

Reduced inhibitory activity has been observed, for example, in *SCN1A*, *TRIO* and *MECP2* model systems. Nav1.1 neuronal sodium channels, encoded by *SCN1A,* are located on GABAergic cortical inhibitory interneurons, with pathogenic variants reducing sodium currents, lowering inhibitory ton and resulting in increased excitation.[178-180] Heterozygous *Scn1a* murine models ($Scn1a^{+/-}$) have also shown significantly lower inhibitory postsynaptic currents and fewer inhibitory synapses, with autistic-like behaviours exhibited by these transgenic models improved through increasing GABAergic activity.[181-183] Murine models of *TRIO* variants with accompanying autism-like behaviours have also been shown to result in reduced inhibitory GABAergic neurotransmission, with both the functional and behavioural phenotype restored through activation of GABA signalling.[184] Finally, *MECP2* variants are involved in a more nuanced picture with wild-type mouse models found to have increased glutamatergic transmission at birth, predominantly due to changes in GABA function, the latter being excitatory during early development but reversing in the first weeks of postnatal development, with this GABA shift delayed in *Mecp2* KO mice, again shifting the excitatory/inhibitory balance to one of overall increased excitatory activity.[185]

Conclusion

We have demonstrated that psychiatric and neurological signs and symptoms frequently co-occur in rare, genetic brain disorders however, lack of consistent phenotyping designed to address both symptom groups has substantially hampered our understanding and interpretation of these overlapping phenotypes. This co-occurrence of symptoms also indicates the potential for overlapping mechanisms, with the evidence outlined above spanning disturbance to synaptic and neuronal structure and function, with subsequent impact on E-I neuronal balance. The impact of these changes across distinct neurodevelopmental stages is also of importance, with potential for symptom emergence and evolution at differing developmental stages, consequent on the same or overlapping pathogenic variants in genes linked by underlying pathophysiological mechanisms. This field requires greater understanding from genetic model systems, spanning animal, invertebrate and cellular models, as well as studies aimed at identification and validation of patient biomarkers. Development of this work will not only be relevant in understanding of these rare disorders, but also place a firmer emphasis on the need for combined investigation of neurological and psychiatric co-morbidity, potentially increasing opportunity for discovery of novel therapeutic targets,

translation of which into the clinical setting may provide treatment opportunity across multiple brain disorders.

References

1 Liu, Y. *et al.* A Selective Review of the Excitatory-Inhibitory Imbalance in Schizophrenia: Underlying Biology, Genetics, Microcircuits, and Symptoms. *Front Cell Dev Biol* **9**, 664535, doi:10.3389/fcell.2021.664535 (2021).

2 Mencacci, N. E. *et al.* Dystonia genes functionally converge in specific neurons and share neurobiology with psychiatric disorders. *Brain* **143**, 2771-2787, doi:10.1093/brain/awaa217 (2020).

3 Cunningham, A. C. *et al.* Movement Disorder Phenotypes in Children With 22q11.2 Deletion Syndrome. *Mov Disord* **35**, 1272-1274, doi:10.1002/mds.28078 (2020).

4 Thygesen, J. H. *et al.* Neurodevelopmental risk copy number variants in adults with intellectual disabilities and comorbid psychiatric disorders. *Br J Psychiatry* **212**, 287-294, doi:10.1192/bjp.2017.65 (2018).

5 Mollon, J., Almasy, L., Jacquemont, S. & Glahn, D. C. The contribution of copy number variants to psychiatric symptoms and cognitive ability. *Mol Psychiatry*, doi:10.1038/s41380-023-01978-4 (2023).

6 Moreno-De-Luca, A. *et al.* Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. *Lancet Neurol* **12**, 406-414, doi:10.1016/S1474-4422(13)70011-5 (2013).

7 Brainstorm, C. *et al.* Analysis of shared heritability in common disorders of the brain. *Science* **360**, doi:10.1126/science.aap8757 (2018).

8 Matsuo, M., Maeda, T., Sasaki, K., Ishii, K. & Hamasaki, Y. Frequent association of autism spectrum disorder in patients with childhood onset epilepsy. *Brain Dev* **32**, 759-763, doi:10.1016/j.braindev.2010.05.005 (2010).

9 Fiest, K. M. *et al.* Depression in epilepsy: a systematic review and meta-analysis. *Neurology* **80**, 590-599, doi:10.1212/WNL.0b013e31827b1ae0 (2013).

10 Scott, A. J., Sharpe, L., Hunt, C. & Gandy, M. Anxiety and depressive disorders in people with epilepsy: A meta-analysis. *Epilepsia* **58**, 973-982, doi:10.1111/epi.13769 (2017).

11 Aaberg, K. M. *et al.* Comorbidity and Childhood Epilepsy: A Nationwide Registry Study. *Pediatrics* **138**, doi:10.1542/peds.2016-0921 (2016).

12 Josephson, C. B. *et al.* Association of Depression and Treated Depression With Epilepsy and Seizure Outcomes: A Multicohort Analysis. *JAMA Neurol* **74**, 533-539, doi:10.1001/jamaneurol.2016.5042 (2017).

13 Hesdorffer, D. C. *et al.* Occurrence and Recurrence of Attempted Suicide Among People With Epilepsy. *JAMA Psychiatry* **73**, 80-86, doi:10.1001/jamapsychiatry.2015.2516 (2016).

14 Berkvens, J. J. *et al.* Autism and behavior in adult patients with Dravet syndrome (DS). *Epilepsy Behav* **47**, 11-16, doi:10.1016/j.yebeh.2015.04.057 (2015).

15 Claes, L. *et al.* De novo SCN1A mutations are a major cause of severe myoclonic epilepsy of infancy. *Hum Mutat* **21**, 615-621, doi:10.1002/humu.10217 (2003).

16 Skluzacek, J. V., Watts, K. P., Parsy, O., Wical, B. & Camfield, P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. *Epilepsia* **52 Suppl 2**, 95-101, doi:10.1111/j.1528-1167.2011.03012.x (2011).

17 Ragona, F. Cognitive development in children with Dravet syndrome. *Epilepsia* **52 Suppl 2**, 39-43, doi:10.1111/j.1528-1167.2011.03000.x (2011).

18 Wolff, M., Casse-Perrot, C. & Dravet, C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. *Epilepsia* **47 Suppl 2**, 45-48, doi:10.1111/j.1528-1167.2006.00688.x (2006).

19 Li, B. M. *et al.* Autism in Dravet syndrome: prevalence, features, and relationship to the clinical characteristics of epilepsy and mental retardation. *Epilepsy Behav* **21**, 291-295, doi:10.1016/j.yebeh.2011.04.060 (2011).
20 Villeneuve, N. *et al.* Cognitive and adaptive evaluation of 21 consecutive patients with Dravet syndrome. *Epilepsy Behav* **31**, 143-148, doi:10.1016/j.yebeh.2013.11.021 (2014).
21 Ouss, L. *et al.* Autism spectrum disorder and cognitive profile in children with Dravet syndrome: Delineation of a specific phenotype. *Epilepsia Open* **4**, 40-53, doi:10.1002/epi4.12281 (2019).
22 Weiss, L. A. *et al.* Sodium channels SCN1A, SCN2A and SCN3A in familial autism. *Mol Psychiatry* **8**, 186-194, doi:10.1038/sj.mp.4001241 (2003).
23 Djemie, T. *et al.* Pitfalls in genetic testing: the story of missed SCN1A mutations. *Mol Genet Genomic Med* **4**, 457-464, doi:10.1002/mgg3.217 (2016).
24 Dibbens, L. M. *et al.* X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat Genet* **40**, 776-781, doi:10.1038/ng.149 (2008).
25 Trivisano, M. *et al.* Defining the electroclinical phenotype and outcome of PCDH19-related epilepsy: A multicenter study. *Epilepsia* **59**, 2260-2271, doi:10.1111/epi.14600 (2018).
26 Kolc, K. L. *et al.* A standardized patient-centered characterization of the phenotypic spectrum of PCDH19 girls clustering epilepsy. *Transl Psychiatry* **10**, 127, doi:10.1038/s41398-020-0803-0 (2020).
27 Vlaskamp, D. R. M. *et al.* Schizophrenia is a later-onset feature of PCDH19 Girls Clustering Epilepsy. *Epilepsia* **60**, 429-440, doi:10.1111/epi.14678 (2019).
28 Weckhuysen, S. *et al.* KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. *Ann Neurol* **71**, 15-25, doi:10.1002/ana.22644 (2012).
29 Milh, M. *et al.* Similar early characteristics but variable neurological outcome of patients with a de novo mutation of KCNQ2. *Orphanet J Rare Dis* **8**, 80, doi:10.1186/1750-1172-8-80 (2013).
30 Millichap, J. J. *et al.* KCNQ2 encephalopathy: Features, mutational hot spots, and ezogabine treatment of 11 patients. *Neurol Genet* **2**, e96, doi:10.1212/NXG.0000000000000096 (2016).
31 Siracusano, M., Marcovecchio, C., Riccioni, A., Dante, C. & Mazzone, L. Autism Spectrum Disorder and a De Novo Kcnq2 Gene Mutation: A Case Report. *Pediatr Rep* **14**, 200-206, doi:10.3390/pediatric14020027 (2022).
32 Kim, E. C. *et al.* Heterozygous loss of epilepsy gene KCNQ2 alters social, repetitive and exploratory behaviors. *Genes Brain Behav* **19**, e12599, doi:10.1111/gbb.12599 (2020).
33 Miceli, F. *et al.* KCNQ2 R144 variants cause neurodevelopmental disability with language impairment and autistic features without neonatal seizures through a gain-of-function mechanism. *EBioMedicine* **81**, 104130, doi:10.1016/j.ebiom.2022.104130 (2022).
34 Carvill, G. L. *et al.* GRIN2A mutations cause epilepsy-aphasia spectrum disorders. *Nat Genet* **45**, 1073-1076, doi:10.1038/ng.2727 (2013).
35 Mangano, G. D. *et al.* De novo GRIN2A variants associated with epilepsy and autism and literature review. *Epilepsy Behav* **129**, 108604, doi:10.1016/j.yebeh.2022.108604 (2022).
36 Lemke, J. R. *et al.* Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes. *Nat Genet* **45**, 1067-1072, doi:10.1038/ng.2728 (2013).
37 Strehlow, V. *et al.* GRIN2A-related disorders: genotype and functional consequence predict phenotype. *Brain* **142**, 80-92, doi:10.1093/brain/awy304 (2019).
38 Li, J. *et al.* De novo GRIN variants in NMDA receptor M2 channel pore-forming loop are associated with neurological diseases. *Hum Mutat* **40**, 2393-2413, doi:10.1002/humu.23895 (2019).

39 Singh, T. *et al.* Rare coding variants in ten genes confer substantial risk for schizophrenia. *Nature* **604**, 509-516, doi:10.1038/s41586-022-04556-w (2022).

40 Allen, N. C. *et al.* Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet* **40**, 827-834, doi:10.1038/ng.171 (2008).

41 Amitai, N. & Markou, A. Disruption of performance in the five-choice serial reaction time task induced by administration of N-methyl-D-aspartate receptor antagonists: relevance to cognitive dysfunction in schizophrenia. *Biol Psychiatry* **68**, 5-16, doi:10.1016/j.biopsych.2010.03.004 (2010).

42 Tarabeux, J. *et al.* Rare mutations in N-methyl-D-aspartate glutamate receptors in autism spectrum disorders and schizophrenia. *Transl Psychiatry* **1**, e55, doi:10.1038/tp.2011.52 (2011).

43 O'Roak, B. J. *et al.* Exome sequencing in sporadic autism spectrum disorders identifies severe de novo mutations. *Nat Genet* **43**, 585-589, doi:10.1038/ng.835 (2011).

44 Gai, X. *et al.* Rare structural variation of synapse and neurotransmission genes in autism. *Mol Psychiatry* **17**, 402-411, doi:10.1038/mp.2011.10 (2012).

45 Rajakulendran, S. *et al.* Genetic and functional characterisation of the P/Q calcium channel in episodic ataxia with epilepsy. *J Physiol* **588**, 1905-1913, doi:10.1113/jphysiol.2009.186437 (2010).

46 Indelicato, E. & Boesch, S. From Genotype to Phenotype: Expanding the Clinical Spectrum of CACNA1A Variants in the Era of Next Generation Sequencing. *Front Neurol* **12**, 639994, doi:10.3389/fneur.2021.639994 (2021).

47 Damaj, L. *et al.* CACNA1A haploinsufficiency causes cognitive impairment, autism and epileptic encephalopathy with mild cerebellar symptoms. *Eur J Hum Genet* **23**, 1505-1512, doi:10.1038/ejhg.2015.21 (2015).

48 van Wamelen, D. J. *et al.* Cross-sectional analysis of the Parkinson's disease Non-motor International Longitudinal Study baseline non-motor characteristics, geographical distribution and impact on quality of life. *Sci Rep* **11**, 9611, doi:10.1038/s41598-021-88651-4 (2021).

49 Ozelius, L. J. *et al.* The early-onset torsion dystonia gene (DYT1) encodes an ATP-binding protein. *Nat Genet* **17**, 40-48, doi:10.1038/ng0997-40 (1997).

50 Bailey, G. A., Rawlings, A., Torabi, F., Pickrell, W. O. & Peall, K. J. Longitudinal analysis of the relationship between motor and psychiatric symptoms in idiopathic dystonia. *Eur J Neurol* **29**, 3513-3527, doi:10.1111/ene.15530 (2022).

51 Wadon, M. E. *et al.* Clinical and genotypic analysis in determining dystonia non-motor phenotypic heterogeneity: a UK Biobank study. *J Neurol* **269**, 6436-6451, doi:10.1007/s00415-022-11307-4 (2022).

52 Doheny, D. O. *et al.* Phenotypic features of myoclonus-dystonia in three kindreds. *Neurology* **59**, 1187-1196, doi:10.1212/wnl.59.8.1187 (2002).

53 Hess, C. W. *et al.* Myoclonus-dystonia, obsessive-compulsive disorder, and alcohol dependence in SGCE mutation carriers. *Neurology* **68**, 522-524, doi:10.1212/01.wnl.0000253188.76092.06 (2007).

54 Peall, K. J., Waite, A. J., Blake, D. J., Owen, M. J. & Morris, H. R. Psychiatric disorders, myoclonus dystonia, and the epsilon-sarcoglycan gene: a systematic review. *Mov Disord* **26**, 1939-1942, doi:10.1002/mds.23791 (2011).

55 Peall, K. J. *et al.* SGCE mutations cause psychiatric disorders: clinical and genetic characterization. *Brain* **136**, 294-303, doi:10.1093/brain/aws308 (2013).

56 Peall, K. J. *et al.* Psychiatric disorders, myoclonus dystonia and SGCE: an international study. *Ann Clin Transl Neurol* **3**, 4-11, doi:10.1002/acn3.263 (2016).

57 van Tricht, M. J. *et al.* Cognition and psychopathology in myoclonus-dystonia. *J Neurol Neurosurg Psychiatry* **83**, 814-820, doi:10.1136/jnnp-2011-301386 (2012).
58 Heiman, G. A. *et al.* Increased risk for recurrent major depression in DYT1 dystonia mutation carriers. *Neurology* **63**, 631-637, doi:10.1212/01.wnl.0000137113.39225.fa (2004).
59 Heiman, G. A. *et al.* Obsessive-compulsive disorder is not a clinical manifestation of the DYT1 dystonia gene. *Am J Med Genet B Neuropsychiatr Genet* **144B**, 361-364, doi:10.1002/ajmg.b.30431 (2007).
60 Liu, D., Cao, H., Kural, K. C., Fang, Q. & Zhang, F. Integrative analysis of shared genetic pathogenesis by autism spectrum disorder and obsessive-compulsive disorder. *Biosci Rep* **39**, doi:10.1042/BSR20191942 (2019).
61 Hahn, H. *et al.* Neurologic and psychiatric manifestations in a family with a mutation in exon 2 of the guanosine triphosphate-cyclohydrolase gene. *Arch Neurol* **58**, 749-755, doi:10.1001/archneur.58.5.749 (2001).
62 Van Hove, J. L. *et al.* Expanded motor and psychiatric phenotype in autosomal dominant Segawa syndrome due to GTP cyclohydrolase deficiency. *J Neurol Neurosurg Psychiatry* **77**, 18-23, doi:10.1136/jnnp.2004.051664 (2006).
63 Tadic, V. *et al.* Dopa-responsive dystonia revisited: diagnostic delay, residual signs, and nonmotor signs. *Arch Neurol* **69**, 1558-1562, doi:10.1001/archneurol.2012.574 (2012).
64 Fuchs, T. *et al.* Mutations in GNAL cause primary torsion dystonia. *Nat Genet* **45**, 88-92, doi:10.1038/ng.2496 (2013).
65 Vuoristo, J. T. *et al.* Sequence and genomic organization of the human G-protein Golfalpha gene (GNAL) on chromosome 18p11, a susceptibility region for bipolar disorder and schizophrenia. *Mol Psychiatry* **5**, 495-501, doi:10.1038/sj.mp.4000758 (2000).
66 Zarrei, M. *et al.* A large data resource of genomic copy number variation across neurodevelopmental disorders. *NPJ Genom Med* **4**, 26, doi:10.1038/s41525-019-0098-3 (2019).
67 Iossifov, I. *et al.* The contribution of de novo coding mutations to autism spectrum disorder. *Nature* **515**, 216-221, doi:10.1038/nature13908 (2014).
68 Tuchman, R. & Rapin, I. Epilepsy in autism. *Lancet Neurol* **1**, 352-358, doi:10.1016/s1474-4422(02)00160-6 (2002).
69 Damasio, A. R. & Maurer, R. G. A neurological model for childhood autism. *Arch Neurol* **35**, 777-786, doi:10.1001/archneur.1978.00500360001001 (1978).
70 Jeste, S. S. The neurology of autism spectrum disorders. *Curr Opin Neurol* **24**, 132-139, doi:10.1097/WCO.0b013e3283446450 (2011).
71 Van Waelvelde, H., Oostra, A., Dewitte, G., Van Den Broeck, C. & Jongmans, M. J. Stability of motor problems in young children with or at risk of autism spectrum disorders, ADHD, and or developmental coordination disorder. *Dev Med Child Neurol* **52**, e174-178, doi:10.1111/j.1469-8749.2009.03606.x (2010).
72 Kanner, L. Autistic disturbances of affective contact. *Acta Paedopsychiatr* **35**, 100-136 (1968).
73 Mouridsen, S. E., Rich, B. & Isager, T. A longitudinal study of epilepsy and other central nervous system diseases in individuals with and without a history of infantile autism. *Brain Dev* **33**, 361-366, doi:10.1016/j.braindev.2010.07.002 (2011).
74 Clarke, D. F. *et al.* The prevalence of autistic spectrum disorder in children surveyed in a tertiary care epilepsy clinic. *Epilepsia* **46**, 1970-1977, doi:10.1111/j.1528-1167.2005.00343.x (2005).

75 Hara, H. Autism and epilepsy: a retrospective follow-up study. *Brain Dev* **29**, 486-490, doi:10.1016/j.braindev.2006.12.012 (2007).

76 Hallmayer, J. *et al.* Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry* **68**, 1095-1102, doi:10.1001/archgenpsychiatry.2011.76 (2011).

77 Cross-Disorder Group of the Psychiatric Genomics, C. *et al.* Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet* **45**, 984-994, doi:10.1038/ng.2711 (2013).

78 Maenner, M. J. *et al.* Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *MMWR Surveill Summ* **69**, 1-12, doi:10.15585/mmwr.ss6904a1 (2020).

79 Ranjan, R. *et al.* Neurological, Psychiatric, and Multisystemic Involvement of Fragile X Syndrome Along With Its Pathophysiology, Methods of Screening, and Current Treatment Modalities. *Cureus* **15**, e35505, doi:10.7759/cureus.35505 (2023).

80 Albizua, I. *et al.* Descriptive analysis of seizures and comorbidities associated with fragile X syndrome. *Mol Genet Genomic Med* **10**, e2001, doi:10.1002/mgg3.2001 (2022).

81 Farzin, F. *et al.* Autism spectrum disorders and attention-deficit/hyperactivity disorder in boys with the fragile X premutation. *J Dev Behav Pediatr* **27**, S137-144, doi:10.1097/00004703-200604002-00012 (2006).

82 Clifford, S. *et al.* Autism spectrum phenotype in males and females with fragile X full mutation and premutation. *J Autism Dev Disord* **37**, 738-747, doi:10.1007/s10803-006-0205-z (2007).

83 Hessl, D. *et al.* Abnormal elevation of FMR1 mRNA is associated with psychological symptoms in individuals with the fragile X premutation. *Am J Med Genet B Neuropsychiatr Genet* **139B**, 115-121, doi:10.1002/ajmg.b.30241 (2005).

84 Bourgeois, J. A. *et al.* Lifetime prevalence of mood and anxiety disorders in fragile X premutation carriers. *J Clin Psychiatry* **72**, 175-182, doi:10.4088/JCP.09m05407blu (2011).

85 Hunter, A. G., Ray, M., Wang, H. S. & Thompson, D. R. Phenotypic correlations in patients with ring chromosome 22. *Clin Genet* **12**, 239-249, doi:10.1111/j.1399-0004.1977.tb00933.x (1977).

86 Wilson, H. L. *et al.* Molecular characterisation of the 22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms. *J Med Genet* **40**, 575-584, doi:10.1136/jmg.40.8.575 (2003).

87 Bonaglia, M. C. *et al.* Disruption of the ProSAP2 gene in a t(12;22)(q24.1;q13.3) is associated with the 22q13.3 deletion syndrome. *Am J Hum Genet* **69**, 261-268, doi:10.1086/321293 (2001).

88 Durand, C. M. *et al.* Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nat Genet* **39**, 25-27, doi:10.1038/ng1933 (2007).

89 Leblond, C. S. *et al.* Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: a gradient of severity in cognitive impairments. *PLoS Genet* **10**, e1004580, doi:10.1371/journal.pgen.1004580 (2014).

90 De Rubeis, S. *et al.* Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations. *Mol Autism* **9**, 31, doi:10.1186/s13229-018-0205-9 (2018).

91 Gauthier, J. *et al.* De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. *Proc Natl Acad Sci U S A* **107**, 7863-7868, doi:10.1073/pnas.0906232107 (2010).

92 Kohlenberg, T. M. *et al.* Psychiatric illness and regression in individuals with Phelan-McDermid syndrome. *J Neurodev Disord* **12**, 7, doi:10.1186/s11689-020-9309-6 (2020).
93 Dingemans, A. J. M. *et al.* The phenotypic spectrum and genotype-phenotype correlations in 106 patients with variants in major autism gene CHD8. *Transl Psychiatry* **12**, 421, doi:10.1038/s41398-022-02189-1 (2022).
94 Douzgou, S. *et al.* The clinical presentation caused by truncating CHD8 variants. *Clin Genet* **96**, 72-84, doi:10.1111/cge.13554 (2019).
95 Doummar, D. *et al.* Childhood-onset progressive dystonia associated with pathogenic truncating variants in CHD8. *Ann Clin Transl Neurol* **8**, 1986-1990, doi:10.1002/acn3.51444 (2021).
96 Splawski, I. *et al.* Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. *Cell* **119**, 19-31, doi:10.1016/j.cell.2004.09.011 (2004).
97 Green, E. K. *et al.* The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. *Mol Psychiatry* **15**, 1016-1022, doi:10.1038/mp.2009.49 (2010).
98 Chen, J., Sun, Y., Liu, X. & Li, J. Identification of a novel mutation in the CACNA1C gene in a Chinese family with autosomal dominant cerebellar ataxia. *BMC Neurol* **19**, 157, doi:10.1186/s12883-019-1381-8 (2019).
99 Heyes, S. *et al.* Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. *Prog Neurobiol* **134**, 36-54, doi:10.1016/j.pneurobio.2015.09.002 (2015).
100 Rodan, L. H. *et al.* Phenotypic expansion of CACNA1C-associated disorders to include isolated neurological manifestations. *Genet Med* **23**, 1922-1932, doi:10.1038/s41436-021-01232-8 (2021).
101 Levy, R. J. *et al.* A Cross-Sectional Study of the Neuropsychiatric Phenotype of CACNA1C-Related Disorder. *Pediatr Neurol* **138**, 101-106, doi:10.1016/j.pediatrneurol.2022.10.013 (2023).
102 Cheadle, J. P. *et al.* Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. *Hum Mol Genet* **9**, 1119-1129, doi:10.1093/hmg/9.7.1119 (2000).
103 Neul, J. L. *et al.* The array of clinical phenotypes of males with mutations in Methyl-CpG binding protein 2. *Am J Med Genet B Neuropsychiatr Genet* **180**, 55-67, doi:10.1002/ajmg.b.32707 (2019).
104 Banerjee, A., Miller, M. T., Li, K., Sur, M. & Kaufmann, W. E. Towards a better diagnosis and treatment of Rett syndrome: a model synaptic disorder. *Brain* **142**, 239-248, doi:10.1093/brain/awy323 (2019).
105 Neul, J. L. *et al.* Developmental delay in Rett syndrome: data from the natural history study. *J Neurodev Disord* **6**, 20, doi:10.1186/1866-1955-6-20 (2014).
106 Leonard, H., Cobb, S. & Downs, J. Clinical and biological progress over 50 years in Rett syndrome. *Nat Rev Neurol* **13**, 37-51, doi:10.1038/nrneurol.2016.186 (2017).
107 Neul, J. L. *et al.* Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol* **68**, 944-950, doi:10.1002/ana.22124 (2010).
108 Peters, S. U. *et al.* Phenotypic features in MECP2 duplication syndrome: Effects of age. *Am J Med Genet A* **185**, 362-369, doi:10.1002/ajmg.a.61956 (2021).
109 Pardinas, A. F. *et al.* Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet* **50**, 381-389, doi:10.1038/s41588-018-0059-2 (2018).

110 Palmer, D. S. *et al.* Exome sequencing in bipolar disorder identifies AKAP11 as a risk gene shared with schizophrenia. *Nat Genet* **54**, 541-547, doi:10.1038/s41588-022-01034-x (2022).
111 Schroder, J. *et al.* Neurological soft signs in schizophrenia. *Schizophr Res* **6**, 25-30, doi:10.1016/0920-9964(91)90017-l (1991).
112 Bachmann, S. & Schroder, J. Neurological Soft Signs in Schizophrenia: An Update on the State- versus Trait-Perspective. *Front Psychiatry* **8**, 272, doi:10.3389/fpsyt.2017.00272 (2017).
113 Chan, R. C. K. *et al.* Neurological soft signs precede the onset of schizophrenia: a study of individuals with schizotypy, ultra-high-risk individuals, and first-onset schizophrenia. *Eur Arch Psychiatry Clin Neurosci* **268**, 49-56, doi:10.1007/s00406-017-0828-4 (2018).
114 Takata, A. *et al.* Loss-of-function variants in schizophrenia risk and SETD1A as a candidate susceptibility gene. *Neuron* **82**, 773-780, doi:10.1016/j.neuron.2014.04.043 (2014).
115 Singh, T. *et al.* Rare loss-of-function variants in SETD1A are associated with schizophrenia and developmental disorders. *Nat Neurosci* **19**, 571-577, doi:10.1038/nn.4267 (2016).
116 Kummeling, J. *et al.* Characterization of SETD1A haploinsufficiency in humans and Drosophila defines a novel neurodevelopmental syndrome. *Mol Psychiatry* **26**, 2013-2024, doi:10.1038/s41380-020-0725-5 (2021).
117 Owen, M. J., Sawa, A. & Mortensen, P. B. Schizophrenia. *Lancet* **388**, 86-97, doi:10.1016/S0140-6736(15)01121-6 (2016).
118 Gecz, J. *et al.* Characterization of the human glutamate receptor subunit 3 gene (GRIA3), a candidate for bipolar disorder and nonspecific X-linked mental retardation. *Genomics* **62**, 356-368, doi:10.1006/geno.1999.6032 (1999).
119 Guilmatre, A. *et al.* Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. *Arch Gen Psychiatry* **66**, 947-956, doi:10.1001/archgenpsychiatry.2009.80 (2009).
120 Wu, Y. *et al.* Mutations in ionotropic AMPA receptor 3 alter channel properties and are associated with moderate cognitive impairment in humans. *Proc Natl Acad Sci U S A* **104**, 18163-18168, doi:10.1073/pnas.0708699104 (2007).
121 Davies, B. *et al.* A point mutation in the ion conduction pore of AMPA receptor GRIA3 causes dramatically perturbed sleep patterns as well as intellectual disability. *Hum Mol Genet* **26**, 3869-3882, doi:10.1093/hmg/ddx270 (2017).
122 Trivisano, M. *et al.* GRIA3 missense mutation is cause of an x-linked developmental and epileptic encephalopathy. *Seizure* **82**, 1-6, doi:10.1016/j.seizure.2020.08.032 (2020).
123 Piard, J. *et al.* The GRIA3 c.2477G > A Variant Causes an Exaggerated Startle Reflex, Chorea, and Multifocal Myoclonus. *Mov Disord* **35**, 1224-1232, doi:10.1002/mds.28058 (2020).
124 Katrancha, S. M. *et al.* Neurodevelopmental disease-associated de novo mutations and rare sequence variants affect TRIO GDP/GTP exchange factor activity. *Hum Mol Genet* **26**, 4728-4740, doi:10.1093/hmg/ddx355 (2017).
125 Kosmicki, J. A. *et al.* Refining the role of de novo protein-truncating variants in neurodevelopmental disorders by using population reference samples. *Nat Genet* **49**, 504-510, doi:10.1038/ng.3789 (2017).
126 Deciphering Developmental Disorders, S. Prevalence and architecture of de novo mutations in developmental disorders. *Nature* **542**, 433-438, doi:10.1038/nature21062 (2017).
127 Ba, W. *et al.* TRIO loss of function is associated with mild intellectual disability and affects dendritic branching and synapse function. *Hum Mol Genet* **25**, 892-902, doi:10.1093/hmg/ddv618 (2016).

128 Barbosa, S. *et al.* Opposite Modulation of RAC1 by Mutations in TRIO Is Associated with Distinct, Domain-Specific Neurodevelopmental Disorders. *Am J Hum Genet* **106**, 338-355, doi:10.1016/j.ajhg.2020.01.018 (2020).
129 Pengelly, R. J. *et al.* Mutations specific to the Rac-GEF domain of TRIO cause intellectual disability and microcephaly. *J Med Genet* **53**, 735-742, doi:10.1136/jmedgenet-2016-103942 (2016).
130 Sadybekov, A., Tian, C., Arnesano, C., Katritch, V. & Herring, B. E. An autism spectrum disorder-related de novo mutation hotspot discovered in the GEF1 domain of Trio. *Nat Commun* **8**, 601, doi:10.1038/s41467-017-00472-0 (2017).
131 De Rubeis, S. *et al.* Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* **515**, 209-215, doi:10.1038/nature13772 (2014).
132 Bourgeron, T. A synaptic trek to autism. *Curr Opin Neurobiol* **19**, 231-234, doi:10.1016/j.conb.2009.06.003 (2009).
133 Sperandeo, A. *et al.* Cortical neuronal hyperexcitability and synaptic changes in SGCE mutation-positive myoclonus dystonia. *Brain*, doi:10.1093/brain/awac365 (2022).
134 Saifee, O., Wei, L. & Nonet, M. L. The Caenorhabditis elegans unc-64 locus encodes a syntaxin that interacts genetically with synaptobrevin. *Mol Biol Cell* **9**, 1235-1252, doi:10.1091/mbc.9.6.1235 (1998).
135 Vardar, G. *et al.* Distinct Functions of Syntaxin-1 in Neuronal Maintenance, Synaptic Vesicle Docking, and Fusion in Mouse Neurons. *J Neurosci* **36**, 7911-7924, doi:10.1523/JNEUROSCI.1314-16.2016 (2016).
136 Mishima, T. *et al.* Syntaxin 1B regulates synaptic GABA release and extracellular GABA concentration, and is associated with temperature-dependent seizures. *J Neurochem* **156**, 604-613, doi:10.1111/jnc.15159 (2021).
137 Zhang, C. *et al.* A neuroligin-4 missense mutation associated with autism impairs neuroligin-4 folding and endoplasmic reticulum export. *J Neurosci* **29**, 10843-10854, doi:10.1523/JNEUROSCI.1248-09.2009 (2009).
138 Tian, C., Paskus, J. D., Fingleton, E., Roche, K. W. & Herring, B. E. Autism Spectrum Disorder/Intellectual Disability-Associated Mutations in Trio Disrupt Neuroligin 1-Mediated Synaptogenesis. *J Neurosci* **41**, 7768-7778, doi:10.1523/JNEUROSCI.3148-20.2021 (2021).
139 Arons, M. H. *et al.* Autism-associated mutations in ProSAP2/Shank3 impair synaptic transmission and neurexin-neuroligin-mediated transsynaptic signaling. *J Neurosci* **32**, 14966-14978, doi:10.1523/JNEUROSCI.2215-12.2012 (2012).
140 Lisman, J. & Raghavachari, S. A unified model of the presynaptic and postsynaptic changes during LTP at CA1 synapses. *Sci STKE* **2006**, re11, doi:10.1126/stke.3562006re11 (2006).
141 Amador, A. *et al.* Modelling and treating GRIN2A developmental and epileptic encephalopathy in mice. *Brain* **143**, 2039-2057, doi:10.1093/brain/awaa147 (2020).
142 Mota Vieira, M. *et al.* An Epilepsy-Associated GRIN2A Rare Variant Disrupts CaMKIIalpha Phosphorylation of GluN2A and NMDA Receptor Trafficking. *Cell Rep* **32**, 108104, doi:10.1016/j.celrep.2020.108104 (2020).
143 Moutin, E. *et al.* Restoring glutamate receptosome dynamics at synapses rescues autism-like deficits in Shank3-deficient mice. *Mol Psychiatry* **26**, 7596-7609, doi:10.1038/s41380-021-01230-x (2021).
144 Jan, Y. N. & Jan, L. Y. Branching out: mechanisms of dendritic arborization. *Nat Rev Neurosci* **11**, 316-328, doi:10.1038/nrn2836 (2010).
145 Wong, R. O. & Ghosh, A. Activity-dependent regulation of dendritic growth and patterning. *Nat Rev Neurosci* **3**, 803-812, doi:10.1038/nrn941 (2002).

146 Llamosas, N. *et al.* SYNGAP1 Controls the Maturation of Dendrites, Synaptic Function, and Network Activity in Developing Human Neurons. *J Neurosci* **40**, 7980-7994, doi:10.1523/JNEUROSCI.1367-20.2020 (2020).
147 Wang, S. *et al.* Loss-of-function variants in the schizophrenia risk gene SETD1A alter neuronal network activity in human neurons through the cAMP/PKA pathway. *Cell Rep* **39**, 110790, doi:10.1016/j.celrep.2022.110790 (2022).
148 Hodges, J. L. *et al.* Astrocytic Contributions to Synaptic and Learning Abnormalities in a Mouse Model of Fragile X Syndrome. *Biol Psychiatry* **82**, 139-149, doi:10.1016/j.biopsych.2016.08.036 (2017).
149 Yan, Q. J., Rammal, M., Tranfaglia, M. & Bauchwitz, R. P. Suppression of two major Fragile X Syndrome mouse model phenotypes by the mGluR5 antagonist MPEP. *Neuropharmacology* **49**, 1053-1066, doi:10.1016/j.neuropharm.2005.06.004 (2005).
150 Comery, T. A. *et al.* Abnormal dendritic spines in fragile X knockout mice: maturation and pruning deficits. *Proc Natl Acad Sci U S A* **94**, 5401-5404, doi:10.1073/pnas.94.10.5401 (1997).
151 Irwin, S. A., Galvez, R. & Greenough, W. T. Dendritic spine structural anomalies in fragile-X mental retardation syndrome. *Cereb Cortex* **10**, 1038-1044, doi:10.1093/cercor/10.10.1038 (2000).
152 Li, X. *et al.* An Autism-Related, Nonsense Foxp1 Mutant Induces Autophagy and Delays Radial Migration of the Cortical Neurons. *Cereb Cortex* **29**, 3193-3208, doi:10.1093/cercor/bhy185 (2019).
153 Xu, Q. *et al.* Autism-associated CHD8 deficiency impairs axon development and migration of cortical neurons. *Mol Autism* **9**, 65, doi:10.1186/s13229-018-0244-2 (2018).
154 Huang, G. *et al.* Uncovering the Functional Link Between SHANK3 Deletions and Deficiency in Neurodevelopment Using iPSC-Derived Human Neurons. *Front Neuroanat* **13**, 23, doi:10.3389/fnana.2019.00023 (2019).
155 Durand, C. M. *et al.* SHANK3 mutations identified in autism lead to modification of dendritic spine morphology via an actin-dependent mechanism. *Mol Psychiatry* **17**, 71-84, doi:10.1038/mp.2011.57 (2012).
156 Zhang, L. *et al.* Altered dendritic morphology of Purkinje cells in Dyt1 DeltaGAG knock-in and purkinje cell-specific Dyt1 conditional knockout mice. *PLoS One* **6**, e18357, doi:10.1371/journal.pone.0018357 (2011).
157 Ophoff, R. A. *et al.* Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell* **87**, 543-552, doi:10.1016/s0092-8674(00)81373-2 (1996).
158 Le Roux, M. *et al.* CACNA1A-associated epilepsy: Electroclinical findings and treatment response on seizures in 18 patients. *Eur J Paediatr Neurol* **33**, 75-85, doi:10.1016/j.ejpn.2021.05.010 (2021).
159 Khosravani, H. & Zamponi, G. W. Voltage-gated calcium channels and idiopathic generalized epilepsies. *Physiol Rev* **86**, 941-966, doi:10.1152/physrev.00002.2006 (2006).
160 Miao, Q. L., Herlitze, S., Mark, M. D. & Noebels, J. L. Adult loss of Cacna1a in mice recapitulates childhood absence epilepsy by distinct thalamic bursting mechanisms. *Brain* **143**, 161-174, doi:10.1093/brain/awz365 (2020).
161 Ernst, W. L., Zhang, Y., Yoo, J. W., Ernst, S. J. & Noebels, J. L. Genetic enhancement of thalamocortical network activity by elevating alpha 1g-mediated low-voltage-activated calcium current induces pure absence epilepsy. *J Neurosci* **29**, 1615-1625, doi:10.1523/JNEUROSCI.2081-08.2009 (2009).

162 Wheeler, D. G. *et al.* Ca(V)1 and Ca(V)2 channels engage distinct modes of Ca(2+) signaling to control CREB-dependent gene expression. *Cell* **149**, 1112-1124, doi:10.1016/j.cell.2012.03.041 (2012).

163 Freir, D. B. & Herron, C. E. Inhibition of L-type voltage dependent calcium channels causes impairment of long-term potentiation in the hippocampal CA1 region in vivo. *Brain Res* **967**, 27-36, doi:10.1016/s0006-8993(02)04190-2 (2003).

164 Moosmang, S. *et al.* Role of hippocampal Cav1.2 Ca2+ channels in NMDA receptor-independent synaptic plasticity and spatial memory. *J Neurosci* **25**, 9883-9892, doi:10.1523/JNEUROSCI.1531-05.2005 (2005).

165 Ali, F. *et al.* Inhibitory regulation of calcium transients in prefrontal dendritic spines is compromised by a nonsense Shank3 mutation. *Mol Psychiatry* **26**, 1945-1966, doi:10.1038/s41380-020-0708-6 (2021).

166 Charlesworth, G. *et al.* Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. *Am J Hum Genet* **91**, 1041-1050, doi:10.1016/j.ajhg.2012.10.024 (2012).

167 Kutschenko, A. *et al.* Functional and Molecular Properties of DYT-SGCE Myoclonus-Dystonia Patient-Derived Striatal Medium Spiny Neurons. *Int J Mol Sci* **22**, doi:10.3390/ijms22073565 (2021).

168 Pederick, D. T. *et al.* Abnormal Cell Sorting Underlies the Unique X-Linked Inheritance of PCDH19 Epilepsy. *Neuron* **97**, 59-66 e55, doi:10.1016/j.neuron.2017.12.005 (2018).

169 Borghi, R. *et al.* Dissecting the Role of PCDH19 in Clustering Epilepsy by Exploiting Patient-Specific Models of Neurogenesis. *J Clin Med* **10**, doi:10.3390/jcm10132754 (2021).

170 Nomura, T. Interneuron Dysfunction and Inhibitory Deficits in Autism and Fragile X Syndrome. *Cells* **10**, doi:10.3390/cells10102610 (2021).

171 Yang, W. P. *et al.* Functional expression of two KvLQT1-related potassium channels responsible for an inherited idiopathic epilepsy. *J Biol Chem* **273**, 19419-19423, doi:10.1074/jbc.273.31.19419 (1998).

172 Simkin, D. *et al.* Dyshomeostatic modulation of Ca(2+)-activated K(+) channels in a human neuronal model of KCNQ2 encephalopathy. *Elife* **10**, doi:10.7554/eLife.64434 (2021).

173 Niday, Z., Hawkins, V. E., Soh, H., Mulkey, D. K. & Tzingounis, A. V. Epilepsy-Associated KCNQ2 Channels Regulate Multiple Intrinsic Properties of Layer 2/3 Pyramidal Neurons. *J Neurosci* **37**, 576-586, doi:10.1523/JNEUROSCI.1425-16.2016 (2017).

174 Kramvis, I. *et al.* Dysregulated Prefrontal Cortex Inhibition in Prepubescent and Adolescent Fragile X Mouse Model. *Front Mol Neurosci* **13**, 88, doi:10.3389/fnmol.2020.00088 (2020).

175 Maltese, M. *et al.* Abnormal striatal plasticity in a DYT11/SGCE myoclonus dystonia mouse model is reversed by adenosine A2A receptor inhibition. *Neurobiol Dis* **108**, 128-139, doi:10.1016/j.nbd.2017.08.007 (2017).

176 Scarduzio, M. *et al.* Strength of cholinergic tone dictates the polarity of dopamine D2 receptor modulation of striatal cholinergic interneuron excitability in DYT1 dystonia. *Exp Neurol* **295**, 162-175, doi:10.1016/j.expneurol.2017.06.005 (2017).

177 Maltese, M. *et al.* Early structural and functional plasticity alterations in a susceptibility period of DYT1 dystonia mouse striatum. *Elife* **7**, doi:10.7554/eLife.33331 (2018).

178 Yu, F. H. *et al.* Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat Neurosci* **9**, 1142-1149, doi:10.1038/nn1754 (2006).

179 Ogiwara, I. *et al.* Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. *J Neurosci* **27**, 5903-5914, doi:10.1523/JNEUROSCI.5270-06.2007 (2007).

180 Hedrich, U. B. *et al.* Impaired action potential initiation in GABAergic interneurons causes hyperexcitable networks in an epileptic mouse model carrying a human Na(V)1.1 mutation. *J Neurosci* **34**, 14874-14889, doi:10.1523/JNEUROSCI.0721-14.2014 (2014).
181 Uchino, K. *et al.* Inhibitory synaptic transmission is impaired at higher extracellular Ca(2+) concentrations in Scn1a(+/-) mouse model of Dravet syndrome. *Sci Rep* **11**, 10634, doi:10.1038/s41598-021-90224-4 (2021).
182 Han, S. *et al.* Autistic-like behaviour in Scn1a+/- mice and rescue by enhanced GABA-mediated neurotransmission. *Nature* **489**, 385-390, doi:10.1038/nature11356 (2012).
183 Catterall, W. A. Dravet Syndrome: A Sodium Channel Interneuronopathy. *Curr Opin Physiol* **2**, 42-50, doi:10.1016/j.cophys.2017.12.007 (2018).
184 Sun, X. *et al.* Dysfunction of Trio GEF1 involves in excitatory/inhibitory imbalance and autism-like behaviors through regulation of interneuron migration. *Mol Psychiatry* **26**, 7621-7640, doi:10.1038/s41380-021-01109-x (2021).
185 Lozovaya, N. *et al.* Early alterations in a mouse model of Rett syndrome: the GABA developmental shift is abolished at birth. *Sci Rep* **9**, 9276, doi:10.1038/s41598-019-45635-9 (2019).

Acknowledgements

The figures have been created with BioRender.com

Author contributions

KJP researched data for the article. All authors contributed substantially to discussion of the content. All authors wrote the article and reviewed and/or edited the manuscript before submission.

Competing Interests

The authors report no competing interests.

Key points box

- Rare, genetic brain disorders frequently involve both neurological and psychiatric phenotypes, although detailed, cross-spectrum clinical phenotyping is rarely undertaken.
- Improved clinical phenotypic understanding of these single gene disorders is key, given the potential for development of genetic model systems, spanning animal, invertebrate and cellular models, aiding understanding of underlying pathophysiological mechanisms.
- Potential shared pathophysiological mechanisms include disruption to synaptic plasticity, synaptic and neuronal structure, balance of excitatory-inhibitory neuronal activity and calcium handling.
- Further mechanistic understanding increases the opportunity for discovery of novel therapeutic targets, potentially providing treatment opportunities across multiple brain disorders.

Table 1: Genetic Neurological disorders with evidence of psychiatric phenotype

Disorder	Gene (OMIM Number)	Inheritance	Encoded protein and function	Age at onset	Neurological phenotype	Psychiatric phenotype	Other Clinical Characteristics
Epilepsy							
	SCN1A (182389)	Autosomal Dominant	Alpha-1 subunit of the voltage-gated sodium channel involved in the generation and propagation of action potentials	First year of life	Multiple epilepsy phenotypes including DS, GEFS+, febrile seizures +, febrile seizures, Sudden Unexpected Death in Epilepsy (SUDEP)	ASD, Severe behavioural problems, including attention-deficit, autistic features, anxiety	Intellectual disability, oculomotor co-ordination deficits
	PCDH19 (300460)	X-linked affecting heterozygous females and mosaic males	Protocadherin-1, a member of the protocadherin family of calcium-dependent, cell-to-cell adhesion molecules	Infancy	Seizures	ADHD, ASD, OCD, schizophrenia.	Intellectual impairment
	KCNQ2 (602235)	Autosomal Dominant	Kv7.2 subunit of the kv7 voltage potassium channel involved in regulating the resting membrane potential (RMP)	Seizures begin in early infancy, sometimes neonatal period.	Overlapping neonatal epileptic phenotypes ranging from self-limited familial neonatal epilepsy (SLFNE) to neonatal-onset developmental and epileptic encephalopathy (NEO-DEE)	ASD, ADHD	Brain imaging shows variable T1- and T2-weighted hyperintensities in the basal ganglia and sometimes thalamus.
	GRIN2A (138253)	Autosomal Dominant	Encodes the GluN2A protein, an isoform of one of two subunits (the other gluN1) that make up NMDAR. NMDAR are glutamate active ion channels found at excitatory synapses in the brain, and are permeable to Na^+, K^+ and Ca^{2+} ions.	Childhood	Childhood epilepsy with centrotemporal spikes, Continuous Spike Waves during Slow Wave Sleep (CSWS), Landau-Kleffner syndrome and atypical benign partial epilepsy of childhood.	ASD, ADHD, Behavioural abnormalities, schizophrenia, bipolar disorder.	Intellectual disability, language delay/impairment, aphasia
	STX1B (601485)	Autosomal Dominant	Syntaxin-1B a core component of the N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex	Infancy, typically <3 years	Febrile or afebrile seizures. Ataxia.	Asperger's syndrome	Global developmental delay and intellectual disability.

	SYNGAP1 (603384)	Autosomal Dominant	brain-specific synaptic Ras GTPase activating protein localized to dendritic spines in neocortical pyramidal neurons. Suppresses signalling pathways linked to NMDAR-mediated synaptic plasticity and AMPAR membrane insertion	Infancy	Variable seizure semiology, hypotonia, ataxia	ASD, impulsivity, mood disturbance	Intellectual disability, microcephaly, dysmorphic facial features
	CACNA1A (601011)	Autosomal Dominant	Alpha1 subunit of the Cav2.1 P/Q-type voltage-gated calcium channel. These channels allow for calcium entry into cells and mediate multiple calcium-dependent processes including neurotransmitter release and gene expression	First hours/days of life	Refractory seizures associated with EEG abnormalities, hypotonia, tremor, ataxia	ADHD, impulsivity, ASD	Global developmental delay, intellectual disability. Loss of function mutations typically result in episodic ataxia 2 or SCA6
	CNTNAP2 (604569)	Autosomal Recessive	Contactin-Associated Protein-Like 2 is a member of the neurexin transmembrane protein group, involved in the neuron-glia interaction and potassium-channel clustering	Infancy	Refractory seizures of variable semiology	ASD, ADHD, Schizophrenia, depression	Intellectual disability, specific language impairment
Dystonia							
	SGCE (604149)	Autosomal Dominant with reduced penetrance owing to maternal imprinting	Epsilon-sarcoglycan protein: single pass transmembrane protein that forms part of the dystrophin-glycoprotein complex linking the intracellular actin cytoskeleton and extracellular space.	Infancy	Upper body predominant myoclonus and dystonia involving neck and UL. LL dystonia sometimes evident in infancy/childhood	Generalised Anxiety Disorder, Social Phobia, Obsessive-Compulsive Disorder, Alcohol excess	CNVs involving SGCE often demonstrate additional clinical traits relating to additional genes involved e.g. joint hypermobility, cerebral cavernomas.
	TOR1A (605204)	Autosomal Dominant with ~30% penetrance	Torsin1A protein, member of the AAA family of adenosine triphosphatases (ATPases) likely involved in multiple cellular activities including synaptic function.	Childhood	Ranging from mild focal dystonia to more severe generalised forms	Recurrent Major Depressive Disorder	-
	GNAL (139312)	Autosomal Dominant	Stimulatory G-alpha subunit of the G protein receptor, highly expressed in	Adulthood – mean age at onset 31.3 years.	Focal dystonia, initial onset typically in cervical region and progressing to	ASD, ADHD	-

			the brain and coupled with D1 dopamine receptors		involve larynx, trunk and limbs		
	ANO3 (610110)	Autosomal Dominant	Anoctamin-3, transmembrane protein within a family of Ca^{2+}-activated chloride channels	Adulthood	Focal dystonia affecting cervical, laryngeal and UL regions, coupled with tremor and myoclonus	-	-
	KMT2B (606834)	Autosomal Dominant	Lysine-specific methyltransferase, responsible for the methylation of multiple forms of histone, inducing gene activation.	Childhood	Progressive dystonia, usually initially in LL, later progressing to involve UL, neck and face.	ASD, ADHD, anxiety, depression	Dysmorphic facies (elongated facies and bulbous nose), short stature, microcephaly, developmental delay.
	GCH1 (600225)	Autosomal Dominant	GTP Cyclohydrolase I, catalyses the conversion of GTP to D-erythro-7,8-dihydroneopterin triphosphate, rate limiting step in synthesis of tetrahydrobiopterin (BH4)	Infancy/Childhood	Dopamine responsive generalised dystonia with diurnal fluctuation. Highly responsive to oral dopaminergic therapy.	Depression, OCD, anxiety	-

Legend: ADHD: Attention Deficit Hyperactivity Disorder, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, ASD: Autism Spectrum Disorder, DS: Dravet Syndrome, GEFS+: Genetic Epilepsy with Febrile Seizures plus, LL: Lower Limbs, NMDAR: N-methyl-D-aspartate Receptor, OCD: Obsessive-Compulsive Disorder, SCA: Spinocerebellar ataxia, UL: Upper Limbs.

Table 2: Genes implicated in psychiatric disorders with evidence of a neurological phenotype

Disorder	Gene (OMIM Number)	Inheritance	Encoded protein and function	Age at onset	Psychiatric phenotype	Neurological phenotype	Other Clinical Characteristics
Autism							
	FMR1 (309550)	X-linked Dominant CCG trinucleotide repeat expansion of 5'UTR FXS >200 CGG repeats FXTAS premutation size repeat (50-200 CGG repeats)	Fragile X mental retardation protein (FMRP), regulates the translation of ~30% of synaptic proteome transcripts	FXS: first 1-2 years of life FXTAS: >50 years, affecting 30-40% of male premutation carriers	FXS: ASD, behavioural disturbance, anxiety, aggression. FXTAS: ASD-related personality traits, affective disorders	FXS: Hypotonia, Seizures FXTAS: late-onset, progressive cerebellar ataxia, intention tremor & cognitive impairment	FXS: intellectual disability, sleep disorders, characteristic craniofacial features (protruding ears, long face), GORD, joint laxity, scoliosis FXTAS: increased risk of thyroid disease, hypertension, neuropathy
	CHD8 (610528)	Autosomal Dominant	Chromodomain Helicase DNA-binding protein that is an ATP-dependent chromatin-remodelling factor that regulates transcription of beta-catenin	Childhood-Adolescence	ASD, abnormal social behaviour	Intellectual disability, hypotonia	Macrocephaly, Pronounced supraorbital ridges, wide-set eyes, broad nose, Gi disturbance (e.g. diarrhoea, constipation), musculoskeletal problems, GU disturbance
	FOXP1 (605515)	Autosomal Dominant	Encodes one of the forkhead box family of transcription factors important in the regulation of gene transcription from early development through to adulthood.	Childhood	ASD, ADHD, anxiety, OCD	Hypotonia, delayed motor development (97%)	Dysmorphic features, intellectual disability, cardiac and urogenital abnormalities Prominent forehead, ptosis, hypertelorism,
	SHANK3 (606230)	Autosomal Dominant	Scaffolding protein enriched in postsynaptic densities of excitatory synapses	Childhood	ASD, possible link with schizophrenia	Hypotonia, gait disturbance, seizures	Delayed speech, dysmorphic features, normal or accelerated growth

	CACNA1C (114205)	Autosomal Dominant	Pore-forming alpha-1C subunit of the long-lasting (L-type) voltage-gated calcium channel CaV1.2	Childhood	ASD, ADHD, anxiety, social problems, aggression, schizophrenia	Hypotonia, seizures	Language delay, skeletal defects, dysmorphic features
	MECP2 (300005)	X-linked Dominant (Rett Syndrome)	Chromatin-associated protein that binds methylated CpGs, activating or repressing transcription.	Infancy	ASD, ADHD	Loss of purposeful hand movements, stereotypic hand movements, spastic paraparesis, seizures, gait abnormalities	Microcephaly, intellectual disability
Schizophrenia							
	SETD1A (611052)	Autosomal Dominant	SET1A is a component of a histone methyltransferase complex involved in regulating transcription	Infancy	Psychotic symptoms, autistic features, anxiety	Hypotonia, seizures	Developmental delay, intellectual disability, delayed speech, dysmorphic facies
	CACNA1G (604065)	Autosomal Dominant	low-voltage-activated Ca(v)3.1 T-type calcium channel highly expressed in cerebellar Purkinje neurons, with T-type Ca2+ channels involved in low threshold calcium spikes	Childhood to adolescence		Axial hypotonia, spasticity, dystonia, cerebellar ataxia	Dysmorphic facial features, microcephaly
	GRIA3 (305915)	X-linked Recessive	AMPA 3, inotropic, glutamate receptor involved in excitatory neurotransmission and synaptic plasticity in thte brain.	Childhood	ASD	Seizures, myoclonic jerks,	Dysmorphic features, distal muscle weakness, intellectual disability
	TRIO (601893)	Autosomal Dominant	Rho Guanine nucleotide Exchange factor (RhoGEF) functioning as a GDP-TO-GTP exchange factor, promoting actin-cytoskeletal reorganisation and thereby contributing to cell migration and growth	Childhood to adolescence	ASD, ADHD, OCD	Hyperreflexia, aphasia, seizures	Intellectual disability, facial dysmorphism. Microcephaly/macrocephaly

Legend: ADHD: Attention Deficit Hyperactivity Disorder, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, ASD: Autism Spectrum Disorder, FXS: Fragile X syndrome, FXTAS: FRAGILE x-associated tremor/ataxia syndrome, GI: Gastrointestinal, GU: Genitourinary, OCD: Obsessive-Compulsive Disorder.

Figure Legends

Figure 1: Venn diagram of overlapping clinical phenotypes including seizures, Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Motor Disorders, Anxiety Depression and Schizophrenia. Blue: genes associated with epilepsy, Green: genes associated with dystonia, Purple: genes associated with ASD, Orange: genes associated with schizophrenia.

Figure 2: Schematic overview of overlapping neuronal and cellular mechanisms that may be contributing to the observed clinical phenotype across rare, genetic brain disorders. A: Details the impact of distinct pathological genetic variants on synaptic receptors and intracellular signalling pathways, B: Indicates the genes in which pathogenic variants have been linked with greater complexity and branching of the dendritic arbor, and those linked with fewer and less well-developed dendritic branching. C: Schematic overview of the channels and intracellular organelles involved in calcium homeostasis and the sites at which pathogenic variants in the genes discussed may disrupt these handling mechanisms.