

The neurodevelopmental spectrum of synaptic vesicle cycling disorders

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Abstract

In this review, we describe and discuss neurodevelopmental phenotypes arising from rare, high penetrance genomic variants which directly influence synaptic vesicle cycling (SVC disorders). Pathogenic variants in each SVC disorder gene lead to disturbance of at least one SVC subprocess, namely vesicle trafficking (e.g. *KIF1A* and *GDI1*), clustering (e.g. *TRIO*, *NRXN1* and *SYN1*), docking and priming (e.g. *STXBP1*), fusion (e.g. *SYT1* and *PRRT2*) or re-uptake (e.g. *DNM1*, *AP1S2* and *TBC1D24*). We observe that SVC disorders share a common set of neurological symptoms (movement disorders, epilepsies), cognitive impairments (developmental delay, intellectual disabilities, cerebral visual impairment) and mental health difficulties (autism, ADHD, psychiatric symptoms). On the other hand, there is notable phenotypic variation between and within disorders, which may reflect selective disruption to SVC subprocesses, spatiotemporal and cell-specific gene expression profiles, mutation-specific effects, or modifying factors. Understanding the common cellular and systems mechanisms underlying neurodevelopmental phenotypes in SVC disorders, and the factors responsible for variation in clinical presentations and outcomes, may translate to personalized clinical management and improved quality of life for patients and families.

KEYWORDS

cerebral visual impairment, epilepsy, intellectual disability, mental health, movement disorders, Synaptic vesicle cycle

1 | INTRODUCTION

Neurodevelopmental disorders encompass diverse, dynamic and interactive childhood-onset symptoms, which can include sensory deficits, motor impairments, epilepsies, intellectual disabilities and mental health difficulties. Until recently, the cause of each individual's disorder was most often unknown. Now, genomic analysis can diagnose a specific cause in 60% of severely affected children

(Gilissen et al., 2014), and the catalogue of genetic diagnoses associated with neurodevelopmental disorders has rapidly expanded to more than 1,500 confirmed genes (<https://www.ebi.ac.uk/gene2 phenotype>). This step-change in aetiological diagnosis yields new opportunities to understand the multi-level mechanisms contributing to each individual's difficulties and, potentially, to treat their underlying brain dysfunction rather than (or in addition to) their on-the-surface symptoms.

Abbreviations: ADHD, attention deficit hyperactivity disorder; CVI, cerebral visual impairment; DD, developmental delay; EEG, electroencephalogram; ID, intellectual disability; MD, movement disorder; MRI, magnetic resonance imaging; PKD, paroxysmal kinesigenic dyskinesia; SVC, synaptic vesicle cycling.

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There are, however, major challenges inherent to these goals. One challenge is the extreme rarity of each genetic diagnosis. A second challenge is the complexity of neurological, cognitive and behavioural symptoms which vary between individuals and within individuals over time, and may be relatively non-specific reflections of underlying neurobiological disruption. One strategy with potential clinical and scientific utility is to consider groups of genetic diagnoses which converge on shared physiological functions, and are thus expected to lead to a similar spectrum of symptoms via common underlying mechanisms. Numerous data-driven analyses have implicated discrete functional networks in neurodevelopmental disorders, such as chromatin regulation, post-synaptic signalling and cytoskeletal architecture (van Bokhoven, 2011; Sullivan, De Rubeis, & Schaefer, 2019). Investigating the phenotypic correlates of functional networks could improve diagnostic confidence, because network-specific "phenotypic signatures" (either overt symptoms or covert endophenotypes) could reduce the number of genetic test results classified as variants of uncertain significance. Network-informed phenotyping could assist in prognostication by expanding the range of types, severities and natural histories of symptoms. Functional networks may also guide clinical management via selection of therapies that are safe and effective network-wide, or novel network-targeted treatments. On the other hand, understanding phenotypic variation within a functional network is also clinically relevant, enabling individualized prognosis and identification of modifiable factors influencing the severity of outcomes.

One such functional network is synaptic vesicle cycling (SVC). SVC genes facilitate and control neurotransmitter release and recycling, and are thus critical for synaptic transmission and plasticity, underlying in-the-moment cognitive processes and adaptive cognitive development. Rare, high penetrance variants in many SVC genes (SVC disorders) have now been diagnosed in individuals with neurodevelopmental disorders (Table 1). In this article we apply the functional networks framework to describe the spectrum of neurodevelopmental phenotypes associated with SVC disorders. Our primary objective is to systematically collate the published clinical literature on SVC disorders, to highlight the extent of similarity across the network, and important differences between and within disorders. Our secondary objective is to provide a quantitative comparison of reported neurodevelopmental phenotypes between SVC disorders and other monogenic developmental disorders. To achieve this, we have analysed open access data from the DECIPHER database (<https://decipher.sanger.ac.uk/>). Considering both sources of information, we discuss reasons for phenotypic similarity and variation within the SVC disorders network.

2 | METHODS

This review encompasses SVC disorders listed by Bonnycastle, Davenport and Cousin in this issue (2020), supplemented by additional disorders with strong evidence for pathogenicity and direct involvement in SVC physiology. Defining the boundaries of a

functional network is not straightforward, and we recognize that some SVC genes will have additional functions which may influence phenotype, for example involvement in post-synaptic physiology or embryonic neurodevelopment. Many other genes will have indirect impact on the SVC, for example via regulation of gene expression and post-translational modification.

We conducted a PubMed search (terms: 'gene name' and VARIANT or MUTATION and NEURODEV* or DISORDER) to identify all publications reporting pathogenic or likely pathogenic variants in each SVC gene alongside clinical phenotype data (ideally at individual patient level). Although we have attempted to collate a comprehensive literature list, this is likely incomplete especially for less rare disorders. Where multiple publications have been pooled into a case review, we report the data from the reviewed case series and aim not to double-report individual cases. We have not conducted independent analysis of the likely pathogenicity of reported variants. For ultra-rare diagnoses where only 1 or a small handful of cases have been reported to date, it is important to maintain caution in presuming pathogenicity. Moreover, it is well-recognized that some SVC genes, for example calcium channel subunits, can be relatively tolerant of coding sequence variation, and assigning pathogenicity to variants (especially missense variants) is challenging. For copy number variants, definitive evidence implicating a dosage-sensitive SVC gene as causative of phenotype is often lacking.

To systematically collate reported phenotypes across publications and across genes, we designed a data extraction spreadsheet (available from corresponding author on request). Tables 2 and 3 compress publication-level data to provide a summary overview of reported neurodevelopmental phenotypes for each SVC disorder. This simplified summary should not devalue the nuanced and detailed work within each individual paper within the reference list. The quantity and granularity of phenotype reporting varies widely between publications, hence empty table cells could mean that a phenotype is truly not observed in patients, or has not been assessed or documented in publications, that is we can only evaluate positive evidence for the presence of phenotypes, and cannot interpret absence of evidence as evidence of absence. The vast majority of reviewed publications represent retrospective case note reviews, rather than comprehensive evaluations applying standardized assessment methods. A further limitation of the literature is that terminology is not consistently applied, for example Human Phenotype Ontology (Kohler et al., 2017) or International League Against Epilepsy classifications (Fisher et al., 2017) are infrequently used, reducing comparability of reporting across studies.

To complement this literature review exercise, we present quantitative analysis of phenotypes reported in DECIPHER (open access) as of December 2019. DECIPHER is used by the clinical community to share and compare phenotypic and genotypic data (Firth et al., 2009). The DECIPHER database currently contains data from 36,122 patients who have given consent for broad data sharing. To facilitate our group-wise analysis, data were shared from DECIPHER in bulk via a data access agreement with the University of Cambridge. Neurodevelopmental Human Phenotype Ontology terms were selected via text search and grouped into four



TABLE 1 Synaptic vesicle cycling disorders

SVC subprocess	Gene (OMIM number)	Protein	Published cases ^a	Decipher variants ^b	Mode of inheritance	Mutation types	References for reviewed publications
Trafficking	KIF1A (601,255)	KINESIN FAMILY MEMBER 1A	34	29	AD, de novo	Missense	(Citterio et al., 2015; Esmaeili Nieh et al., 2015; Hamdan et al., 2011; Lee et al., 2015; Ohba, Haginoya, & Osaka, 2015; Ylikallio et al., 2015)
	AP4S1 (607,243)	ADAPTOR-RELATED PROTEIN COMPLEX 4, SIGMA-1 SUBUNIT	8	2	AR	Nonsense; Frameshift; Splice site	(Abou Jamra et al., 2011)
	AP4E1 (607,244)	ADAPTOR-RELATED PROTEIN COMPLEX 4, EPSILON-1 SUBUNIT	2	1	AR	Partial deletion; Truncating; Frameshift	(Moreno-De-Luca et al., 2011)
	RPH3A (612,159)	RABPHILIN 3A	1	0	AR	Missense	(Maselli et al., 2018)
	GDI1 (300,104)	GDP DISSOCIATION INHIBITOR 1	57	1	XLD, inherited or de novo	Missense; Frameshift; CNV	(Bienvenu, des Portes, V., Saint Martin, & A., 1998; D'Adamo et al., 1998; Pinto, Delaby, & Merico, 2014; Strobl-Wildemann et al., 2011; Vandewalle et al., 2009; Ward et al., 2018)
Clustering and scaffolding	TRIO (617,061)	TRIPLE FUNCTIONAL DOMAIN	30	34	AD, de novo	Deletion; Frameshift; Missense; Nonsense	(Ba, Yan, & Reijnders, 2016; Barbosa et al., 2020; de Ligt et al., 2012; Pengelly, Greville-Heygate, & Schmidt, 2016)
	BSN (604,020)	BASSOON PRESYNAPTIC CYTOMATRIX PROTEIN	3	0	AD, de novo	Microdeletion	(Eto, Sakai, & Shimada, 2013; Haldeman-Englert et al., 2009)
	MINT2/APBA2 (602,712)	AMYLOID BETA A4 PRECURSOR PROTEIN-BINDING, FAMILY A, MEMBER 2	7	0	AD, de novo or inherited	Missense; CNV	(DiFrancesco et al., 2019; Peycheva, Kamenarova, & Ivanova, 2018)
	NRXN1 (600,565)	NEUREXIN I	135	11	AD, de novo or inherited	Exonic deletion; Missense	(Bena et al., 2013; Dabell et al., 2013; Lowther et al., 2017; Al Shehhi et al., 2019; Rochtus et al. 2019)
	NRXN2 (600,566)	NEUREXIN II	11	12	AD, inherited	Frameshift; Missense	(Gauthier et al., 2011)
	PCLO (604,918)	PICCOLO PRESYNAPTIC CYTOMATRIX PROTEIN	4	2	Autosomal recessive	Missense	(Ahmed et al., 2015)
	SYN1 (313,440)	SYNAPSIN I	28	5	XLD	Missense; Nonsense	(Fassio et al., 2011; Gauthier et al., 2011; Guarnieri et al., 2017)
Docking and priming	SYN2 (600,755)	SYNAPSIN II	4	0	AD (females unaffected)	Missense; Nonsense	(Corradi et al., 2014)
	UNC13A (609,894)	UNC13 HOMOLOG A	1	0	AD, de novo	Missense	(Lipstein et al., 2017)

(Continues)

TABLE 1 (Continued)

SVC subprocess	Gene (OMIM number)	Protein	Published cases ^a	Decipher variants ^b	Mode of inheritance	Mutation types	References for reviewed publications
Fusion	STXBP1 (602,926)	SYNTAXIN-BINDING PROTEIN 1	180	38	AD, de novo (rarely, AR)	Missense; Frameshift; Truncating	(Gburek-Augustat et al., 2016; Lammertse et al., 2020; O'Brien et al., 2019; Parrini, Marini, & Mei, 2017; Stamberger et al., 2016; Uddin, Woodbury-Smith, & Chan, 2017; Valence et al., 2019)
	CPLX1 (605,032)	COMPLEXIN 1	3	0	AR	Nonsense	(Redler et al., 2017)
	RIMS1 (606,629)	PROTEIN REGULATING SYNAPTIC MEMBRANE EXOCYTOSIS 1	2	0	AD, de novo	Frameshift	(Dong et al., 2014; Peter et al., 2019)
	RIMS3 (611,600)	PROTEIN REGULATING SYNAPTIC MEMBRANE EXOCYTOSIS 3	6	0	AD, inherited	Missense	(Kumar et al., 2010)
	SYT1 (185,605)	SYNAPTOTAGMIN 1	11	2	AD, de novo	Missense	(Baker et al., 2015, 2018)
	VAMP2/SYB (185,881)	VESICLE-ASSOCIATED MEMBRANE PROTEIN 2/ SYNAPTOSOMAL-ASSOCIATED PROTEIN, 25-KD	10	0	AD, de novo; AR	Missense; Frameshift; Deletion	(Salpietro, Lin, & Delle Vedove, 2017; Salpietro et al., 2019; Shen et al., 2017)
	STX1A (186,590)	SYNTAXIN 1A	1	0	AD inherited	Missense	(Cartier et al., 2015)
	STX1B (602,926)	SYNTAXIN 1B	30	2	AD, de novo	Truncation, In-frame insertion, Deletion	(Schubert et al., 2014; Vlaskamp et al., 2016)
	SNAP25 (600,322)	SYNAPTOSOMAL-ASSOCIATED PROTEIN, 25-KD	8	5	AD, de novo	Missense	(Fukuda et al., 2018; Heyne et al., 2018; Rohena et al., 2013; Shen, Selcen, Brengman, & Engel, 2014)
	PRRT2 (614,386)	PROLINE-RICH TRANSMEMBRANE PROTEIN 2	>200	1	AD, de novo or inherited (Rarely, AR)	Truncating; Insertion; Frameshift; Deletion	(El Achkar, Rosen Sheidley, O'Rourke, Takeoka, & Poduri, 2019; Chen et al., 2011; Delcourt et al., 2015; Ebrahimi-Fakhari, Saffari, Westenberger, & Klein, 2015; Heron et al., 2012; Li, Zhu, & Wang, 2012; Pavone et al., 2019; Vlaskamp et al., 2019; Wang et al., 2011)
	CAMK2A (114,078)	CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE II-ALPHA	21	8	AD, de novo	Missense; Deletion	(Akita, Aoto, & Kato, 2018; Chia et al., 2018; Kury et al., 2017)
	CAMK2B (607,707)	CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE II-BETA	10	8	AD, de novo	Missense; Insertion; Deletion	(Akita et al., 2018; Kury et al., 2017)
	CACNA2D1 (114,204)	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, ALPHA-2/DELTA SUBUNIT 1	6	0	AD, inherited	Deletion	(Mefford et al., 2011; Vergult et al., 2015)

(Continues)



TABLE 1 (Continued)

SVC subprocess	Gene (OMIM number)	Protein	Published cases ^a	Decipher variants ^b	Mode of inheritance	Mutation types	References for reviewed publications
	CACNA1A (617,106)	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT	37	29	AD de novo (or mosaic)	Missense	(Jodice et al., 1997; Epi, 2016; Reinson et al., 2016; Romaniello et al., 2010; Tonelli et al., 2006; Yue, Jen, Nelson, & Baloh, 1997)
	CACNA1C (114,205)	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1C SUBUNIT	21	10	AD, de novo	Recurrent missense (G406R); Deletion	(Mio et al., 2020; Splawski et al., 2004)
	CACNA1D (114,206)	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, L TYPE, ALPHA-1D SUBUNIT	5	8	AD, de novo	Missense	(Hofer et al., 2020; Pinggera et al., 2015; Scholl et al., 2013)
	CACNA1E (618,285)	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, ALPHA-1E SUBUNIT	30	10	AD, de novo	Missense	(Helbig et al., 2018)
	CACNA1H (607,904)	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, T TYPE, ALPHA-1H SUBUNIT	14	1	AD, de novo or inherited	Missense	(Chen et al., 2003)
	DNM1 (602,377)	DYNAMIN 1	34	13	AD, de novo	Missense; Nonsense	(Nakashima et al., 2016; Deciphering Developmental Disorders 2017; von Spiczak et al., 2017; Brereton et al., 2018)
Endocytosis	SYP (313,475)	SYNAPTOPHYSIN	18	2	XLR	Missense; Truncating	(Harper, Mancini, van Slegtenhorst, & Cousin, 2017; Tarpey et al., 2009)
	AP1S2 (300,629)	ADAPTOR-RELATED PROTEIN COMPLEX 1, SIGMA-2 SUBUNIT	39	0	XLR	Nonsense; Splice site	(Cappuccio et al., 2019; Huo, Teng, Wang, & Liu, 2019; Tarpey et al., 2006)
	RAB11A (605,570)	RAS-ASSOCIATED PROTEIN RAB11A	4	3	AD, de novo	Missense	(Hamdan et al., 2017)
	RAB11B (604,198)	RAS-ASSOCIATED PROTEIN RAB11B	5	4	AD, de novo	Missense	(Laners et al., 2017)
	TBC1D24 (613,577)	TBC1 DOMAIN FAMILY, MEMBER 24	62	0	AR and AD	Missense; Frameshift; Nonsense	(Balestrini et al., 2016; Banuelos et al., 2017; Lozano et al., 2016; Mucha et al., 2019; Strazisar, Neubauer, Paro Panjan, & Writzl, 2015)
	SYNJ1 (604,297)	SYNAPTOJANIN 1	7	0	AR	Missense (recurrent variant)	(Hardies et al., 2016; Krebs, Karkheiran, & Powell, 2013; Olgiati, De Rosa, & Quadri, 2014; Quadri, Fang, & Picillo, 2013)
	CLTC (118,955)	CLATHRIN, HEAVY POLYPEPTIDE	4	15	AD, de novo	Frameshift, Missense	(DeMari et al., 2016; Hamdan et al., 2017) (Manti et al., 2019)

^aTotal number of individuals with neurodevelopmental disorder and variant in gene of interest, in reviewed publications.^bNumber of open access sequence variants in DECIPHER (www.decipher.sanger.ac.uk) accessed December 2019. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive; XLD, X-linked dominant; CNV, Copy Number Variant.

TABLE 2 SVC disorders – Intellectual, behavioural, psychiatric and visual impairments

Gene	Developmental delay or ID	ASD	ADHD	Other behavioural and psychiatric features	Visual impairment
Vesicle trafficking	KIF1A	Always	Mild to severe	Sometimes	Often Optic nerve atrophy, CVI
	AP4 subunits	Always	Severe to profound		Sometimes
	RPH3A	N = 1	Mild		
	GDI1	Often	Females – mild Males - mild to severe	Sometimes Hyperactivity	Sometimes Esotropia
Scaffolding and Clustering	TRIO	Always	Borderline to severe	Sometimes	Sometimes Strabismus
	BSN	Always	Mild to moderate	Sometimes	Sometimes CVI, pale fundi
	MINT2/ APBA2	Sometimes	Mild to severe		
	NRXN1/2	Often	Normal range to severe	Sometimes	Sometimes Strabismus, acuity, cataracts, retinopathy
	PCLO	Always	Severe		Sometimes Pale optic discs
	SYN1	Often	Borderline to severe	Sometimes	
	SYN2	Sometimes	Speech delay	Always	
	STXBP1	Always	Mild to profound	Sometimes	Sometimes Strabismus
Docking and priming	UNC13A	N = 1	Moderate	Present	
	CPLX1	Always	Severe delay		
	RIMS1	Always	Variable	Sometimes	Sometimes Anxiety, depression
	RIMS3	Always	Moderate	Sometimes	Often Mood disorders, anxiety, OCD

(Continues)

TABLE 2 (Continued)

	Gene	Developmental delay or ID	ASD	ADHD	Other behavioural and psychiatric features	Visual impairment
Fusion	SVT1	Always	Severe to profound	Hyperkinetic episodes	Often Episodic agitation	Often Esotropia, CVI
	VAMP2/SYB	Always	Moderate to severe	Often		Unknown CVI
	STX1A		Cohort ascertained for ASD			
	STX1B	Always	Mild to severe	Sometimes	Sometimes Compulsions, aggression	
	SNAP25	Often	Borderline to severe	Sometimes Inattention		Sometimes Cerebellar eye signs
	CACNA2D1	Always	Mild to moderate		Often Not specified	
	CACNA1 subunits	Often	Mild to severe	Sometimes		Often Strabismus, nystagmus
	CAMK2A, B	Always	Mild to severe	Sometimes	Often Irritability, anxiety, self-injury	Sometimes Reduced acuity, strabismus, CVI
	PRRT2	Rarely	Borderline to severe	Sometimes	Sometimes Unspecified challenging behaviour, neuropsychiatric problems	Sometimes Visual aura, gaze palsy, strabismus, nystagmus.
Endocytosis	DNM1	Always	Mild to profound	Sometimes	Often Self-injury, agitation, aggression, anxiety	Sometimes CVI
	SYP	Always	Mild to severe			Sometimes
	AP152	Always	Mild to profound	Sometimes Hyperactivity	Often Aggression, self-injury	Sometimes Esotropia
	RAB11A, B	Always	Moderate to profound	Sometimes	Sometimes Aggression	Sometimes Hypermetropia, strabismus, nystagmus, CVI, optic atrophy
	TBC1524	Always	Mild to severe	Sometimes	Sometimes Psychotic symptoms, mood disorders	Sometimes Various
	SYNJ1, 2	Sometimes	Mild to Profound		Sometimes Irritability	Often CVI, vertical gaze limitation, eyelid apraxia
	CLTC	Always	Mild to severe	Sometimes	Sometimes Mood disorders, anorexia	Sometimes Nystagmus, cataracts

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CVI, cerebral visual impairment. Protein name for each gene is listed in Table 1; ID, intellectual disability; OCD, obsessive compulsive disorder.

Always = reported to be present in all cases; Often = reported to be present in more than 50% of cases; Sometimes = reported to be present in less than 50% cases; Empty box = not reported (no comment on phenotype within publication OR positive comment that phenotype not present).

TABLE 3 SVC disorders – Movement disorders, epilepsies, neuroimaging and clinical neurophysiology

SVC subprocess	Gene	Movement disorders and neurological signs			Epilepsy			Typical age of onset	MRI	EEG
		Frequency	Types	Typical age of onset	Frequency	Types	Typical age of onset			
Vesicle trafficking	KIF1A	Sometimes	Axial hypotonia, hyperreflexia, spasticity, ataxia, athetosis, tremor	Infancy to early childhood	Sometimes	Diverse		Often progressive cerebral and cerebellar atrophy	Unspecified abnormalities	
	AP4 subunits	Sometimes	Cerebral palsy, hyperreflexia, hypertonia	Infancy	Often	Generalized tonic-clonic seizures		Ventriculomegaly cerebellar atrophy, abnormal white matter	Generalized low-frequency background activity	
	RPH3A	Always	Myaesthesia, dyssynergia, ataxia, tremor	Early childhood				Normal	Normal	
	GDI1	Sometimes	hypotonia, spasticity, motor stereotypies, unsteady gait		Sometimes	Absence seizures, febrile seizures	Infancy	Normal or mild non-specific	Normal or abnormal background	
Scaffolding and Clustering	TRIO	Sometimes	Tremor, hypotonia, ataxic gait		Sometimes	Nocturnal seizures, or unspecified				
	BSN	Always	Hypotonia, ataxic gait	Infancy	Often	Febrile seizure, status epilepticus	Infancy	Non-specific white matter abnormalities	Abnormal (unspecified)	
	MINT2/APBA2	Sometimes	Hypotonia		Always	Generalized or focal				
	NRXN 1, 2, 3	Often	Hypotonia, hyporeflexia, ataxia		Sometimes	Diverse generalized seizure types	Infancy or early childhood	Normal or mild to moderate atrophy		
	PCLO	Often	Hypotonia		Always	Generalized	-	Pontocerebellar hypoplasia		
	SYN1, 2				Sometimes	Generalized and complex partial seizures	Throughout childhood	Diffuse atrophy	Normal interictal	
Docking and Priming	STXBP1	Sometimes	Hypotonia, ataxia, tremor, spasticity, dyskinesia, dystonia (rarely)		Often	Diverse, including early epileptic encephalopathy, later focal or generalized seizures	Can be neonatal or later in infancy or childhood	Normal or mild non-specific	Focal and multifocal epileptiform activity, disorganized background	
	UNC13A	Present n = 1	Dyskinesia, hyperkinesia, tremor	Soon after birth	Present n = 1	Febrile seizures		Normal	Normal	
	CPLX1	Sometimes	Cerebral palsy	Early childhood	Always	Migrating myoclonic epilepsy, generalized seizures	Infancy	Normal or mild non-specific	Ictal and interictal epileptiform features	

(Continues)



TABLE 3 (Continued)

SVC subprocess	Gene	Movement disorders and neurological signs			Epilepsy			MRI	EEG
		Frequency	Types	Typical age of onset	Frequency	Types	Typical age of onset		
	RIMS1,3	Sometimes							
Fusion	SYT1	Often	Hypotonia, dystonia, chorea, athetosis, hyperkinesia, ataxia, stereotypies	Early childhood	Never			Normal or mild non-specific	Bursts of low-frequency oscillations, posterior dominant
	VAMP2	Always	Hypotonia, hyperkinesia, Stereotypies, myaesthesia	Neonatal to early childhood	Often	Infantile spasms, focal seizures, status epilepticus	Neonatal to childhood	Normal or mild non-specific	high-voltage delta activity, sharp wave-slow-wave complexes
	STX1A								
	STX1B				Often	Diverse generalized, myoclonic, astatic	Infancy to old age	Mild cerebellar atrophy in 2 patients.	Low-frequency background; multifocal spikes.
	SNAP25	Often	Tremor, ataxia, hypotonia, joint contracture, myaesthesia		Always	Diverse generalized types	Infancy to childhood	Normal or mild non-specific	Generalized polyspike and wave discharges; background diffuse slowing.
	CACNA2D1	Often	Ataxia	Early childhood	Always	Generalized, complex partial, atonic, myoclonic astatic	Infancy to early childhood	Usually normal	Multifocal spikes and spike complexes
	CACNA1 subunits	Often	Hypotonia, ataxia, dystonia, chorea, dyskinesia, hyperkinesia, hyporeflexia, tremor, episodic ataxia, migraine	Mid-childhood onwards	Sometimes	Highly diverse	Infancy to early childhood	Normal or mild non-specific	Multifocal discharges, hypsarrhythmia, slow spike-wave
	CAMK2 A and B	Often	Hypotonia, hyperkinetic-dystonic stereotypies, ataxia, oculogyric crisis	Infancy	Sometimes	Highly diverse including myoclonic, complex partial and generalized seizures	Infancy to childhood	Normal or mild non-specific	Focal or multifocal discharges
	PRRT2	Often	Paroxysmal kinesigenic dyskinesia, dystonia, chorea-athetosis	5–18 years	Sometimes	Benign familial infantile epilepsy, infantile convulsions and choreoathetosis, other non-specific types	Usually infancy but can be later onset	Normal	Focal spike activity, usually normal interictal

(Continues)



TABLE 3 (Continued)

SVC subprocess	Gene	Movement disorders and neurological signs			Epilepsy			MRI	EEG
		Frequency	Types	Typical age of onset	Frequency	Types	Typical age of onset		
Endocytosis	DNM1	Often	Choreoathetosis, dystonia		Often	Highly diverse	Infancy	Normal or mild non-specific	Bursts of low-frequency oscillations, nonspecific background slowing.
	SYP	Sometimes	Ataxia, hypotonia, restless movements	From infancy	Sometimes	Unspecified			
	AP1S2	Sometimes			Sometimes	Unspecified	Childhood		
	RAB11 A, B	Sometimes	Dystonia, spasticity		Often	infantile spasms, myoclonic seizures, focal seizures.	Infancy	Extensive white matter hypoplasia	Abnormal background activity
	TBC1D24	Sometimes	Ataxia, dystonia, dyskinetic hand movements, hearing loss		Often	Highly diverse including myoclonic, complex partial and generalized seizures	Infancy and early childhood	Normal or mild non-specific	Diverse interictal and ictal abnormalities, or normal
	SYNJ1, 2	Sometimes	Progressive spastic quadriplegia, hypertonic, dystonia	Infancy	Often	Early onset refractory generalized or focal seizures	Infancy	Normal or generalized cerebral atrophy	Hypsarrhythmia or multifocal epileptic activity, slow background
	CLTC	Sometimes	Hyporeflexia, ataxia, hypokinetic-rigid syndrome, bradykinesia		Sometimes	Diverse and often pharmacoresistant seizures	Late infancy - early childhood	Normal or non-specific progressive atrophy	Normal or epileptiform spikes

Note: Always = reported to be present in all cases; Often = reported to be present in more than 50% of cases; Sometimes = reported to be present in less than 50% cases; Empty box = not reported (no comment on phenotype within publication OR positive comment that phenotype not present). Protein name for each gene is listed in Table 1.

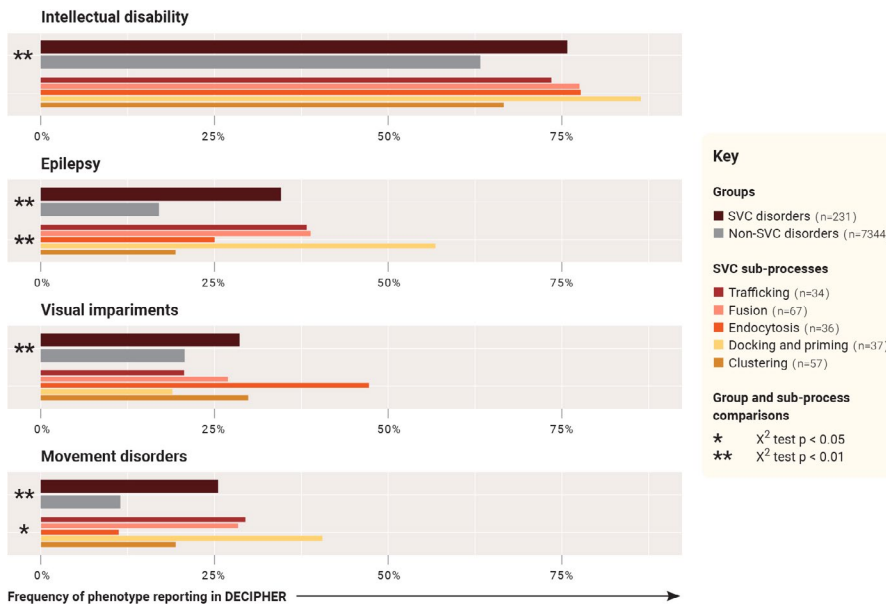


FIGURE 1 Comparison of neurodevelopmental phenotype frequencies for SVC and non-SVC disorders. Neurodevelopmental phenotype frequencies for open access sequence variants in SVC and non-SVC genes, reported in the DECIPHER database as of December 2019. See text for statistical analyses

categories (developmental delay/ intellectual disability, movement disorders, epilepsies, visual impairments) reflecting the symptom domains most frequently reported in the SVC disorders literature review. There is likely under-reporting of phenotype presence within DECIPHER, since there is no requirement to positively affirm every possible phenotype when reporting a variant to the database. Hence frequencies should be interpreted in comparative terms, and not as prevalence statistics. It should also be noted that many individual patients within DECIPHER have more than one sequence variant. Reported phenotype frequencies were compared between sequence variants in SVC genes and all other developmental disorder genes (not copy number variants; classified by the uploading clinical team as pathogenic, likely pathogenic or uncertain) (Figure 1). SVC subprocess variants within DECIPHER were also compared, grouped according to Bonnycastle, Davenport, and Cousin (2020) according to predominant roles in vesicle trafficking, clustering and scaffolding, docking and priming, fusion and endocytosis.

In the following sections, we summarize and discuss the results of our literature review and DECIPHER analysis, organized by phenotype domain, ordered by the frequency of phenotype reporting in DECIPHER. For each phenotype domain, we provide a description of symptoms, discuss frequency and variability in symptoms within SVC disorders, and highlight genotype–phenotype correlations and neural systems mechanisms where these are known.

3 | DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY

Intellectual disability (ID) is defined as significant and persistent impairments in cognitive ability and adaptive function, with onset before the age of 18 years (APA, 2013). ID is commonly preceded by, though not an inevitable successor to, delay in achieving developmental milestones (DD), either globally or selectively within motor,

communication and social domains. DD and ID are the hallmark functional consequences of any disruption or constraint on brain development; they are of high clinical importance in predicting the needs of patients and families, but low specificity with regard to aetiology and mechanism.

Our literature review indicated that DD/ID is reported in all SVC disorders, but varies in prevalence from being universally reported in around two thirds of disorders, to only sometimes or rarely reported in the remainder. This was corroborated within DECIPHER, where DD or ID was reported for 75% of SVC cases, in comparison to 63% of non-SVC cases ($\chi^2(1) = 14.49, p < .001$). Determining the true prevalence of DD/ID in association with SVC disorder variants is difficult, because these phenotypes are the primary ascertainment criteria for many individuals referred for genetic testing, but are exclusion criteria for some cohort studies focused on specific phenotypes, for example autism (Nakamura et al., 2008) or epilepsy (DiFrancesco et al., 2019). Across the SVC disorders catalogue, DD/ID varies in severity from mild to profound. For some genes, for example *CPLXN1*, *SYT1* and *VAMP2*, DD/ID has always been reported as severe or profound. However, for the majority of SVC disorders, severity of DD/ID can range from mild to profound. There are a number of caveats here, one being that initial discovery of novel genetic disorders tends to take place in severely affected individuals; once a larger number of cases are identified genotype-first, it is common to observe a broadening of the severity range for DD/ID. In addition, clinical literature does not consistently apply the same criteria for classifying ID severity, and this classification can change over time within individuals.

It is also interesting to consider SVC disorders, notably *PRRT2*, which are not usually associated with DD/ID. The cognitive consequences of *PRRT2* variants have received limited attention to date, but include learning disabilities and impaired fine motor skills, alongside neuropsychiatric difficulties in some individuals (Djemie et al., 2014). One possibility is that *PRRT2* variants exerting a more

severe impact on SVC fusion capacity may be lethal, hence de novo cases are rarely diagnosed and inherited cases may represent the tolerable mutation spectrum. However, it is also possible that co-occurring cognitive and mental health difficulties arise because of secondary causes in some individuals with *PRRT2* variants (such as second genetic hits, or consequential to infantile epilepsy), and that *PRRT2* dysfunction is not directly related to cognitive impairment, for reasons not currently understood. Discovering why *PRRT2*-related SVC disruption usually results in relatively intact cognitive development may be relevant to other SVC disorders.

To date, there are very few studies that have employed standardized assessments to characterize DD/ID in more detail within SVC disorders (either observational methods, or direct assessment using neuropsychological tests feasible for individuals with milder impairments). We reported questionnaire-based assessment of adaptive function and behavioural characteristics in 14 individuals with *STXBP1* variants, and found that on average global impairment was more severe than other monogenic neurodevelopmental disorders, with particularly severe restriction to receptive language, social skills and fine motor abilities (O'Brien et al., 2019). Several other authors have reported that speech abilities may be disproportionately affected in SVC disorders. For example *GDI1* dosage variants have been associated with pronounced speech delay, even among individuals with milder ID or no ID (Ward et al., 2018). Similarly, speech delays are present in over 90% of individuals with *NRXN1* deletions, even among those with normal range intelligence (Al Shehhi et al., 2019; Bena, Bruno, & Eriksson, 2013; Dabell, Rosenfeld, & Bader, 2013). However, comparative longitudinal research is needed to determine whether the trajectories of communication development are more homogeneous and severe among the SVC disorders group than expected for any other neurodevelopmental disorders group.

The extent to which SVC diagnoses are associated with progressive neuropathology and decline in cognition and adaptive function over time cannot yet be concluded (although it has been noted for some conditions, e.g. dominant *KIF1A* variants). This potential for decline is an understandable worry for affected individuals and their families, however, recognizing dynamic or deteriorating symptoms may help to define treatment priorities and identify opportunities for positive clinical impact.

Overall, current data indicate that while DD/ID is a common functional consequence of SVC disruption, it is not inevitable, and is variable between individuals and over time. This variability prompts the major questions of how SVC disruption constrains the emergence of cognitive capacities, and which factors predict and mediate variation in cognitive outcomes. Our literature review did not highlight a strong association between SVC subprocesses and ID prevalence or severity, and within Decipher we did not observe significant differences between subprocess groups in the frequency of DD/ID ($\chi^2(4) = 5.18, p = .269$). We reviewed individual disorder studies for evidence of modifying factors. There is currently no positive evidence that the presence or severity of epilepsy is a major mediating factor for DD/ID within SVC disorders, for example within the *STXBP1* group in which both epilepsy severity and DD/ID severity

are highly variable (Stamberger, Nikanorova, & Willemsen, 2016). Second-hit genomic modifiers of outcome have yet to be explored in any SVC disorder.

A small number of genotype–phenotype studies indicate that variation in molecular disruption can underlie variation in cognitive outcomes within SVC disorders. At the most basic level, both heterozygous and biallelic loss of function mutations have been reported for some genes (e.g. *STXBP1*, *CACNA1A*, *PRRT2*); for these ultra-rare cases, homozygosity is associated with ID severity (Delcourt, Riant, & Mancini, 2015; Lammertse et al., 2020; Reinson, Oiglane-Shlik, & Talvik, 2016). Domain-specific predictors of ID severity have been reported for *DNM1*, where PH domain variants are associated with a milder phenotype than GTPase or middle domains variants (Nakashima, Kouga, & Lourenco, 2016; von Spiczak, Helbig, & Shinde, 2017). *TRIO* missense mutations at spectrin sites are associated with more severe ID compared to missense mutations at GEFD1 site or nonsense mutations, translating to hyper/hypoactivation of RAC1 (Barbosa et al., 2020). However, SVC physiological correlates of these genotype–phenotype associations remain unknown. For *SYT1*, there have been early attempts to relate the severity of vesicle release dysfunction to patients' functional outcomes including ID. Baker et al. (2018) showed that variants I368T and N371K have a quantitatively more severe impact on rate of vesicle release than variants D366E and D304G, mirroring patients' severity of cognitive outcome. These results have recently been replicated in independent experiments and extended to show a graded dominant-negative effect of *SYT1* dysfunction on post-synaptic activation (Bradberry et al., 2020). Building on these findings, it is possible that impairment to SVC kinetics and neurotransmission efficiency (via diverse molecular mechanisms specific to each gene) could mediate cognitive impairment and influence ID severity across the SVC functional network. In summary, to prognosticate regarding ID severity for individuals with SVC disorders, it is necessary to go beyond the gene to consider the specific mutation and its consequence on protein function and physiology.

4 | EPILEPSY

A seizure is a transient occurrence of symptoms and/or signs because of abnormal excessive or synchronous neuronal activity in the brain, and an individual is defined as having epilepsy if they have an enduring predisposition to seizures, having experienced at least one (Fisher et al., 2014). Diagnosis rests on careful assessment of clinical phenomena and supporting electrophysiological evidence from electroencephalography (EEG). Epilepsy classification now encompasses seizure types, co-morbidities and aetiologies (Fisher et al., 2017), with the aim of better prognosticating and targeting treatments to reduce seizure frequency, reduce risk of life-threatening complications, reduce risk of neurotoxicity secondary to prolonged seizure activity and hypoxia (status epilepticus), and minimize side-effects of anti-epileptic drugs especially when used in combination for prolonged periods. Understanding epilepsy from a genetic perspective

is clearly important, if knowledge of associated epilepsy phenotypes and mechanisms could improve epilepsy management and impact on long-term outcomes. However, seizures are a complex manifestation of many interacting neurobiological factors including age, brain structural integrity, metabolic status and environmental triggers (e.g. temperature, diet, infection, sensory stimulation). Thus predicting an individual's seizure risk, seizure types, treatment response and likelihood of remission based on genetic diagnosis alone may not be realistic. However, there is potential benefit in exploring whether SVC disorders share seizure susceptibility mechanisms and whether this has implications for epilepsy management.

Our literature review found that epilepsy has been diagnosed in at least some individuals with 27 out of 33 SVC disorders. Epilepsy is a universal feature in 5 SVC disorders, and for the remainder prevalence of epilepsy is variable (from rare to affecting the majority of individuals). It is also notable that some SVC disorders have never been associated with seizures to date (e.g. *RIMS1/3* and *SYT1*), despite electrophysiological abnormalities on EEG. Elevated risk of epilepsy in comparison with other developmental disorders was confirmed via DECIPHER analysis: seizures or epilepsy were reported for 35% of SVC variants compared with 17% of non-SVC variants ($\chi^2(1) = 46.98, p < .001$). Establishing the true prevalence of epilepsy is complex, because of the age-dependent nature of seizures—some genes (notably *PRRT2*) are associated with a typical infantile age of seizure onset followed by remission, whereas others are associated with unpredictable age of onset and prognosis (meaning that seizures may not be present at the time of genetic diagnosis and reported in the literature or to DECIPHER). There is also a likely bias towards ascertainment for epilepsy-affected individuals in genetic discovery cohorts. Over time, it is becoming clear that some disorders initially associated with severe and persistent epilepsy risk (e.g. *STXBP1*) are actually associated with a much more variable epilepsy phenotype, which can remit or not present until older age. However, it does appear that SVC disorders carry an elevated seizure susceptibility, in keeping with the presumed electrophysiological origins of neurodevelopmental symptoms.

Epilepsy phenotypes reported across the SVC disorders group and within each individual disorder are highly diverse, encompassing all types of focal-onset and generalized seizures, that is SVC disruption can disturb local or global excitability, leading to a myriad of seizure phenomena. What is less clear (and beyond the scope of this review) is whether the pathophysiology underlying vulnerability to seizures, and the mechanisms of seizure initiation, progression and termination, are common and distinct to SVC disorders. Some clues may come from EEG characteristics. Epileptiform EEG features observed in SVC disorder individuals correlate with observed seizure phenotypes. However, interictal abnormalities and background EEG abnormalities point towards distinctive and unusual electrophysiological properties, including bursts of low-frequency oscillations, which have been observed across a number of disorders (*AP4* subunit variants, *STXBP1*, *STX1B*, *SYT1* and *DNM1*). However, the relationships between these abnormal synchronizations and seizure risk are not clear. This is particularly unclear for variants in *SYT1* in which

profoundly abnormal EEG oscillations are characteristic, but seizures have not been reported for any patient to date.

Genotype–phenotype studies are potentially informative of mechanisms contributing to variable epilepsy risk across the SVC spectrum. For example Balestrini, Milh, and Castiglioni (2016) reported more severe and drug-resistant epilepsies in individuals with frameshift, nonsense and splice site variants versus missense variants in *TBC1D24*. In contrast, dominant-negative missense variants in *SNAP25*, *DNM1* and calcium channel subunits are associated with severe epilepsy phenotypes (Helbig et al., 2018; Heyne et al., 2018; von Spiczak et al., 2017). For some genes, a domain-specific genotype–phenotype correlation for epilepsy has been detected, for example *VAMP2* C-terminal region (Salpietro et al., 2019). There is likely to be diversity of mechanisms by which genotypes mediate variation in epilepsy risk within SVC disorders. For example epilepsy-associated mutations may impact on early neurite development, as has been shown for *SYN1* (Fassio et al., 2011), *TBC1D24* (Balestrini et al., 2016) and *STXBP1* (Yamashita, Chiyonobu, & Yoshida, 2016), whereas seizure risk might be lower for variants impacting only on post-embryological SVC function.

We explored within the DECIPHER dataset whether SVC subprocesses could predict prevalence, and potentially highlight epilepsy-relevant mechanisms. Subprocess groups differed significantly in frequency of epilepsy reporting ($\chi^2(4) = 16.11, p = .003$), being highest in the docking and priming subgroup, and lowest in the clustering group (where prevalence was in line with non-SVC variants). The docking subgroup is dominated by *STXBP1* variants, hence ascertainment and reporting bias should be considered as a potential limiting factor in interpreting this observation. It has been reported that *STXBP1* haploinsufficiency reduces inhibitory neurotransmission of GABA-ergic interneurons (Kovacevic et al., 2018), hence future studies of seizure mechanisms in SVC disorders may need to focus on selective impact on inhibitory neurotransmitter systems (either embryological neurodevelopment or postnatal function). In addition to selective impact on SVC subprocesses, involvement in trans- and post-synaptic zone processes may contribute to variable epilepsy risk. Until mechanisms are better understood, epilepsy management in SVC disorders is likely to remain empirically driven by epilepsy phenotypes and safety profiles, and a significant proportion of individuals will continue to suffer from refractory seizures.

5 | VISUAL IMPAIRMENTS

Visual function is critical to accessing and interacting with the environment. Any impairments to vision (whether arising from the eye, visual tracts, primary visual cortex or vision-relevant neural systems) will influence diverse aspects of learning, adaptive function and social interaction. In the absence of structural eye abnormalities or retinopathy (both rare among individuals with SVC disorders) abnormal visual behaviour is presumed to arise from Cerebral Visual Impairment (CVI). CVI is itself a broad descriptive spectrum encompassing diverse visual processing problems, which can be very difficult to assess in the



context of extensive cognitive impairments. CVI commonly co-occurs with developmental motor impairments, for example in the context of periventricular white matter pathology secondary to prematurity and hypoxia. CVI is less well documented in genetic neurodevelopmental disorders, but it is increasingly recognized that some genetic disorders are associated with higher prevalence of CVI than expected for level of global neurodevelopmental impairment (Bosch et al., 2016). If SVC disorders are associated with CVI (alongside motor and cognitive impairments, or as an isolated problem), this is important to recognize because adapting individuals' visual environment and educational support can promote many other positive aspects of development, in particular communication skills and emotional stability. Ultimately, strategies to directly improve cerebral visual information processing could also be beneficial.

Our literature review highlighted a visual phenotype in 21 out of 33 SVC disorders. We noted that visual phenotypes were reported infrequently for disorders of docking and priming, but were reported for all disorders of endocytosis and almost all disorders of fusion and trafficking. Moreover, there appeared to be some broad differences in the types of visual symptoms most commonly associated with SVC subprocesses—for disorders of trafficking, fusion and endocytosis, eye movement abnormalities and CVI appear to be especially common. This summary of the literature was mirrored within the DECIPHER database—we found that visual phenotypes were reported more commonly for SVC variants than non-SVC variants (29% versus 21%; $\chi^2(1) = 7.98$, $p = .005$). We also detected contrasting frequencies of visual impairments between SVC subprocess groups, being especially common within the endocytosis subprocess group (>40%), although subprocess groups did not differ significantly overall ($\chi^2(4) = 9.03$, $p = .060$). Within DECIPHER, most endocytosis-related variants are within *DNM1*, *CLTC* and *RAB11A*, and this reported frequency of visual impairments is consistent with our review of the literature on these three genes. One potential reporting bias to note is that visual impairments may be more commonly assessed if they have already been noted in the published literature.

Why might it be the case that SVC disorders are associated with an elevated rate of CVI in comparison to other neurogenetic disorders? One possibility could be co-occurrence with movement disorders, either because these two phenotype categories arise from an overlapping set of neuroanatomical systems functionally susceptible to SVC disruption (e.g. sensorimotor integration cortex and subcortical-cortical feedback systems), or because motor impairments have a consequential impact on eye movement control and higher-order visual development. Within the SVC disorders group in DECIPHER, there is only marginal difference in the rate of reported visual impairment between individuals with (33%) and without (28%) a movement disorder, indicating that these two phenotype domains are not tightly associated. Another possibility is that visual impairments could co-occur with epileptogenic abnormalities of excitability, or arise as a secondary consequence of seizure activity. However, the rate of reported visual impairment was identical (29%) among SVC disorder individuals in DECIPHER with and without reported epilepsy. In summary, visual impairment appears to be an independent

symptom domain within the SVC group. While multiple aspects of SVC physiology can affect vision, the impact of disrupted endocytosis on sensory plasticity and vision-relevant neural systems development may be a particularly interesting avenue to explore.

6 | MOVEMENT DISORDERS

Movement disorders (MD) encompass many different types of abnormal involuntary motor symptoms including dystonia, chorea-athetosis, myoclonus, tremor, ataxia and stereotypies. Symptoms can be continuous or paroxysmal, acute or chronic, hypokinetic or hyperkinetic, part of a complex neurodisability or isolated. Although MD and delayed motor skill acquisition are not synonymous, involuntary movements can impede practical activities ranging from ambulation to fine motor skills, and have knock-on consequences for cognitive and social development, educational inclusion and mental health. It can be difficult to distinguish MD from epileptic or behavioural abnormalities, especially when these co-occur within the same individual. For example it may not always be possible to distinguish between hyperkinetic involuntary movements and attention deficit hyperactivity disorder (ADHD), or stereotypies and autism-related repetitive mannerisms, since there is no definitive discriminating neurobiological test. Discriminating between epileptic and non-epileptic origins of symptoms (e.g. myoclonic movement disorder versus myoclonic seizures) can usually be resolved via EEG. An additional complicating factor for ascertaining the prevalence of movement disorder is that symptoms vary across the lifespan within individuals, a common pattern being infant hypotonia followed by childhood dystonia and chorea, and later progression to hypertonia and hypokinesia. In general terms, MD arise from abnormal cortical-subcortical network activity arising from dysfunctional basal ganglia or cerebellar control systems (and/or cortex in case of myoclonus). In many MD aetiologies, structural damage or white matter pathology can be identified on magnetic resonance imaging (MRI). However, as listed in Table 3, subcortical structural pathology (either congenital or degenerative) is not reported on routine MRI for any SVC disorder, and only mild and non-specific cerebral or cerebellar atrophy or white matter maturational differences have been reported, indicating a functional rather than structural origin to MD symptoms.

At least one type of movement disorder has been reported in 26 out of 33 SVC disorders, making it one of the most common presenting neurological features across the SVC functional network. Literature review indicated that disorders of clustering and scaffolding carry lower risk of MD (although with exceptions such as *KIF1A*). Disorders of docking and priming, including *STXBP1*, are rarely associated with severe dystonia and dyskinesia, but tremor and ataxia are common. For disorders of fusion and endocytosis, mixed involuntary movement symptoms are reported in association with almost every gene, but vary in frequency, type and severity within disorders. *PRRT2* is perhaps an exception, in that variants are associated with a very characteristic movement disorder phenotype (paroxysmal kinesigenic dyskinesia, PKD—recurrent brief attacks

of involuntary movements, triggered by movement), but also other episodic phenomena including hemiplegic migraine and ataxia (intriguingly overlapping with *CACNA1A*). Dangerous escalations of sustained involuntary movements (known as dystonic storms, status dystonicus or oculogyric crises), which can be associated with autonomic and cardiorespiratory collapse, are infrequently reported across the SVC disorders spectrum.

Within the DECIPHER database we searched for reporting of dystonia, chorea, tremor, ataxia, gait disturbance and stereotypies, finding that at least one of these symptoms was reported for 26% of SVC gene variants compared with 11% of non-SVC variants ($\chi^2(1) = 41.25, p < .001$). Hence, although MD are not specific to SVC genes, and do not affect all individuals, this phenotype category is significantly enriched in association with SVC disorders. In keeping with our overview of the literature, we found significant difference in likelihood of MD reporting between SVC subprocesses ($\chi^2(4) = 10.03, p = .040$), but with risk being highest for the docking and trafficking subgroups. Looking in more detail, we found that the high rate of MD for these two subgroups represents tremor, ataxia and stereotypies, whereas dystonia is reported relatively frequently for fusion and endocytosis genes. This suggests that disturbance to different aspects of SVC impacts on different neural systems necessary for motor control.

There are few genotype–phenotype studies focused on movement disorder symptoms within SVC disorders. Despite extensive investigation and the presence of recurrent variants, *PRRT2* variants do not appear to predict PKD severity, with high levels of intra-familial variation including non-penetrance (Valtorta, Benfenati, Zara, & Meldolesi, 2016). For *SYT1*, dyskinetic movement disorder was reported in association with some, but not all recurrent mutations (observed in multiple individuals with I368T and N371K, but not D366E) which may reflect a threshold effect or graded impact of disruption to exocytosis (Baker et al., 2018; Bradberry et al., 2020). A single patient with dyskinetic movement disorder has been reported with a de novo P814L variant in *UNC13A* (Lipstein et al., 2017). Electrophysiological studies in murine neuronal cultures and functional analysis in *C. elegans* showed that the *UNC13A* variant causes a distinctive dominant gain of function characterized by an increased fusion rate of vesicles. Hence variants in two fusion genes (*SYT1* and *UNC13A*) seem to have opposing effects on neurotransmission kinetics, leading to a similar movement disorder, indicating the complexity of presynaptic regulation of motor control.

In summary, both literature review and DECIPHER analysis highlight the elevated prevalence of MD in SVC disorders in comparison to other monogenic causes of neurodevelopmental disorder. This confirms that subcortical-cortical network function is dependent on tight pre-synaptic control of neurotransmission. However, the variation in symptom prevalence and types, between and within disorders, highlights the complexity of motor control and potential availability of compensatory mechanisms capable of buffering SVC dysfunction. The high frequency of tremor and ataxia in association with vesicle trafficking may reflect broader transport defects influencing white matter tract development (indeed *KIF1A* is relatively

highly expressed within white matter). For docking genes such as *STXBP1*, a cerebellar mechanism appears more likely, based on relatively high regional expression. The specific neural systems origin of involuntary movements in individuals with fusion and endocytosis disorders remain to be discovered. One possibility is that midbrain dopaminergic cells may be selectively dependent on SVC disorder genes (e.g. lacking synaptotagmin isoform expression to compensate for *SYT1* dysfunction), leading to inefficient dopaminergic signalling and basal ganglia function. Another possibility is that abnormal temporal dynamics of neurotransmission has a system-specific impact on neural networks underlying voluntary control of movement. Another explanation is that SVC disorders are associated with a general state of hyper-excitability, over-tipping the balances between action execution and action inhibition. Defining the mechanisms underlying these symptoms is important, as each mechanism suggests a different mode of treatment, for example specific pharmacological targeting of a neurotransmitter system, or specific anatomical targeting via deep brain stimulation. Defining these mechanisms and identifying safe and effective treatments for MD in SVC disorders could be relevant to later onset degenerative conditions resulting in convergent symptom profiles, and involving a functionally similar genetic spectrum in familial and early onset cases (most notably *SYNJ1* and *SNCA*).

7 | MENTAL HEALTH

Individuals with neurodevelopmental disorders carry an elevated vulnerability to disturbances of emotion regulation, social interaction and behavioural control, resulting in higher rates of mental health difficulties across the lifespan (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Emerson & Hatton, 2007). These difficulties are important because they have major impact on quality of life for patients and their families, and predict long-term support needs. However, mental health difficulties are not an inevitable consequence of ID, and do not in general correlate with severity of global cognitive impairments. Each mental health symptom (such as anxiety, mood disturbance or social withdrawal) can arise from a host of different neurobiological and cognitive mechanisms, and the symptoms arising from an underlying vulnerability can be equally diverse. However, it may be that individuals sharing a genetic diagnosis, or in this case sharing SVC network disruption, also share a more homogeneous set of underlying vulnerabilities and associated symptoms. To better understand and manage mental health difficulties in individuals with SVC disorders, it would be ideal to integrate information about each individual's genetic diagnosis, their neurobiological vulnerabilities and cognitive impairments, and their environmental and interpersonal risk factors.

Within the reviewed literature on SVC disorders, childhood-onset psychiatric phenotypes (predominantly autism or ADHD) have been reported in 24 out of 33 SVC disorders (Table 2). As expected, neither of these behaviourally defined diagnoses is universally reported for all cases of any SVC disorder (excepting studies where



autism was the ascertaining criterion). Within DECIPHER, mental health phenotypes are not extensively documented, but we did not find that autism was reported more frequently for the SVC disorders group (7.36%) in comparison to all other disorders (8.46%). However, the complexity of SVC-associated neurodevelopmental phenotypes is likely to introduce several challenges in the assessment and diagnosis of social, emotional and behavioural difficulties. For example cerebral visual impairment and autism are both frequently reported in association with *DNM1* variants—determining the origins and significance of symptoms such as abnormal eye contact or auditory hypersensitivity may be difficult if not impossible in this context. Similarly, it can be very difficult in clinical practice to discriminate between neurological symptoms (such as hyperkinetic involuntary movement disorder or motor stereotypies), and mental health symptoms (such as hyperactivity and repetitive behaviours), all of which are common features of SVC disorders. In fact, these different terminologies may reflect identical symptom phenomenon, or disruption to the same neurobiological mechanisms, but varying in degree. It is noteworthy that mental health diagnoses appear to be especially common in SVC disorders associated with a milder range of ID (such as *TRIO*, *NRXN* and *CLTC* variants). This may reflect a greater clinical sensitivity to atypical behavioural profiles in these groups as compared to severe and profound impairment, or less comprehensive support and resources available to those with milder ID, or true specificity.

The majority of SVC gene discovery studies have focused on children, hence the longer term psychiatric morbidity across the network has yet to be established. This is especially true for de novo disorders where affected individuals across multiple generations of a family will not be available. Where adult cases have been described, for example de novo variants in *TRIO* (Barbosa et al., 2020) or inherited variants in *GDI1* (Ward et al., 2018), it is clear that emotional and social vulnerabilities in individuals with SVC disorders do extend beyond the childhood and adolescent periods. Indeed, a wide range of later onset psychiatric diagnoses have been reported across 21 different SVC disorders, such as depression, anxiety, obsessive compulsive disorder and psychosis.

Each psychiatric diagnosis encompasses a diverse range of symptoms and impairments (for autism—diverse aspects of social function plus restricted and repetitive behaviours; for ADHD—inattention, hyperactivity and impulsivity; for mood disorders—highly diverse emotional and somatic symptoms). Current literature on SVC disorders does not enable us to establish associations with specific symptom dimensions, because few studies have reported this level of information, or compared SVC disorders to other neurodevelopmental disorder groups. Self-injury, agitation and aggression can be particularly distressing and challenging for patients and carers, and appear to be relatively prevalent among the SVC disorders group. More positively, we found that strong social motivation and enjoyment of family relationships was a frequent characteristic of individuals with *STXBP1* variants, and distinguished this group from other individuals with non-SVC disorders and ID of similar severity (O'Brien et al., 2019). Future studies are required to determine if

these features (both problematic and positive) are observed more commonly among individuals with SVC disorders than in other groups with severe ID, visual impairments and movement disorders.

We cannot identify any study to date which provides evidence for genotype–phenotype correlations within an SVC disorder for the presence or specific characteristics of autism or psychiatric disorders. Our literature review did not highlight any clear associations between SVC subprocesses and likelihood of mental health manifestations. Nor was there sufficient reporting of psychiatric phenotypes within the DECIPHER database to meaningfully relate SVC subprocesses to this clinical domain. Investigating the neurodevelopmental pathways from SVC disturbance to mental health difficulties could be of great clinical value for individuals with SVC disorders, and for a proportion of individuals in the general population with similar symptoms, arising via a similar mechanistic pathway.

8 | CONCLUDING COMMENTS

In this review we have discussed the neurodevelopmental features of SVC disorders, organized by symptom domains. In reality it is unusual to observe isolated symptoms from a single domain—most individuals will experience a complex combination of interacting symptoms and impairments across domains, which will change over time. Although no single symptom discussed in this review is unique or pathognomonic, in combination they may be indicative of a possible SVC disorder. The specificity of these observations will be increased if SVC disorders can be compared to other synaptic disorders, or to other groups presenting with similar neurodevelopmental phenotypes, rather than all genetic causes of developmental disorder combined. Physical complications involving the gastrointestinal, respiratory and autonomic systems have not been discussed here—they are reported in a number of SVC disorders, usually in association with severe neurodisability, and it is not clear whether they occur more frequently than expected for global neurodevelopmental impairment. Peripheral neurological symptoms have also not been surveyed.

We are currently witnessing the first generation of SVC disorder diagnoses—while variants in these genes must always have occurred, only a small number of diagnoses have yet been made, and only in the limited economic and cultural circumstances where genomic testing is currently available. Hence we are at a very early stage of documenting the complete clinical spectrum, and important uncertainties remain. Prospective natural history studies are needed to obtain a comprehensive phenotypic evidence-base which can assist with clinical interpretation of variants, prognostication and management. Families and clinicians are increasingly motivated to integrate genetic diagnosis with each individual's unique phenotypic kaleidoscope, to harness knowledge of underlying mechanisms and select personalized treatments, aiming to improve immediate quality of life and promote long-term wellbeing.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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