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REVIEW

Clinician's guide to genes associated with Rett-like phenotypes—Investigation of a Danish cohort and review of the literature

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The differential diagnostics in Rett syndrome has evolved with the development of next generation sequencing-based techniques and many patients have been diagnosed with other syndromes or variants in newly described genes where the associated phenotype(s) is yet to be fully explored. The term Rett-like refers to phenotypes with distinct overlapping features of Rett syndrome where the clinical criteria are not completely fulfilled. In this study we have combined a review of Rett-like disorders with data from a Danish cohort of 35 patients with Rett-like phenotypes emphasizing the diagnostic overlap with Pitt-Hopkins syndrome, Cornelia de Lange syndrome with *SMC1A* variants, and epileptic encephalopathies, for example, due to *STXBP1* variants. We also found a patient with a pathogenic variant in *KCNB1*, which has not been previously linked to a Rett-like phenotype. This study underlines the clinical and genetic heterogeneity of a Rett syndrome spectrum, and provides an overview of the Rett syndrome-related genes described to date, and hence serves as a guide for diagnosing patients with Rett-like phenotypes.

KEYWORDS

atypical Rett, *CDKL5*, *FOXG1*, *KCNB1*, *MECP2*, Rett-like, RTT, *SMC1A*

1 | INTRODUCTION

The neurodevelopmental disorder Rett syndrome (RTT) was first described in 1966 by Dr Andreas Rett, who reported 22 girls with loss of speech and hand use, and who developed hand stereotypies.[1] Apart from the classical/typical form (RTT) there are atypical forms of RTT (atypical RTT) with different clinical subgroups such as "preserved speech variant,"[2] the "early seizure variant"[3,4] and the "congenital variant,"[5] Today, the term Rett-like is used when there is an overlapping phenotype with typical or atypical RTT, but in whom the

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clinical criteria are not fulfilled. There are to date no formal published consensus criteria for a Rett-like diagnosis, and thus this description can be given to any patient with different combinations of the distinct features of RTT.

The genetic causes of typical RTT, atypical RTT and Rett-like disorders have been intensely studied. Typical RTT patients almost exclusively have pathogenic *MECP2* variants,[6] while atypical RTT and Rett-like patients show genetic heterogeneity. The most common genes involved apart from *MECP2* are: *CDKL5* (cyclin-dependent kinase-like 5), in which variants cause the early onset seizure disorder[7] and *FOXG1*, which is responsible for the congenital RTT variant.[8] Several additional new genes have been suggested to be associated with atypical RTT and a Rett-like disorder.[9–12] These studies have also revealed previously unrecognized clinical similarities of Rett spectrum phenotypes with other neurodevelopmental disorders. One of the unexpected findings has been the identification of *SMC1A* variants, which are traditionally linked to Cornelia de Lange syndrome (CdLS), in Rett-like patients.[13] Furthermore, several Rett-like patients have pathogenic variants in epileptic encephalopathy genes.[14] From a clinical perspective these findings enable an improved comprehension of the genetic landscape of atypical RTT and Rett-like disorders, potentially transforming the primary clinical diagnosis to a genetic one. From a research perspective, the genetic landscape is yet to completely unfold, and some of the genes associated with these phenotypes may be linked through similar functional pathways.

In this study, we present a genetic review of a Rett-like spectrum (typical RTT, atypical RTT and Rett-like disorder) and our findings in a Danish Rett-like cohort, including association of the epilepsy gene, *KCNB1*, as a new Rett-like gene. The purpose of this review is to provide a guide for molecular diagnosis of patients with Rett-like phenotypes.

2 | RETT SYNDROME

RTT is mainly seen in females and presents with only a few neurodevelopmental symptoms before the age of 6 to 18 months.[15] A period of regression will then occur, and abilities especially related to hand function and speech can deteriorate or be lost altogether.[16] Hand stereotypies are a main feature and the patients often have severely impaired functional use of their hands.[17] Another distinct clinical feature often present which can help to point to the diagnosis is the breathing abnormalities (including hyperventilation and/or breath holding episodes).[18] Patients all have intellectual disability (ID). Other features that often develop over time include progressive microcephaly[19] and epilepsy (occurring in approximately 68% at a mean age of 4.7 years).[20,21] Scoliosis is also very common.[16] Facial dysmorphism is not distinct, but few have subtle dysmorphic facial features which do not enable a clinical diagnosis.[22]

Today the international diagnostic criteria published in 2010[23] are used to assist in establishing the clinical diagnosis of RTT (listed in Table 1). RTT patients should have 4 main criteria (partial or complete loss of purposeful hand movements, partial or complete loss of spoken language, a gait abnormality, and stereotypic hand movements); while a diagnosis of atypical RTT is suggested if the patient has 2 or more of the main in addition to 5 or more of the supportive criteria.[23] Both forms are characterized by a period of developmental regression followed by recovery or stabilization. In addition, the presence of any of the following features excludes a diagnosis of typical or classic RTT: a brain injury, a neurometabolic disease or neurological infection, and abnormal psychomotor development with an onset before the age of 6 months.[23]

2.1 | The Rett syndrome genes

MECP2, encoding methyl CpG binding protein 2, is the major gene related to RTT and there are over 4600 *MECP2* variants (pathogenic, benign, or with unknown significance) described in the literature.[24] *MECP2* variants mainly cause RTT (including classical/typical and variant/atypical RTT), but may rarely also be associated with non-syndromic neurodevelopmental disorders including autism.[25]

Variants in *CDKL5* have been reported in about 500 patients[24] and the most notable clinical feature of patients with pathogenic mutations of this gene is early onset epilepsy. These patients have ID and progressive microcephaly.[26] Stereotypic hand movements, respiratory impairment with breath holding and hyperventilation, and severely impaired speech, hand function and gait may also be observed.[27,28] These features are suggestive of RTT, but normal development during the first 6 months is rare in these patients and they often have facial dysmorphic features.[29,30] Traditionally, the term Hanefeld or early onset epilepsy variant of RTT[4,26] has been used for this diagnosis, but recently the term CDKL5 disorder has been introduced and is considered as a separate clinical disorder from RTT.[31]

FOXG1 variants are less common (approximately 80 cases in total[29]) and neurodevelopmental impairment is already observable in early infancy. As *FOXG1* is located on chromosome 14, variants affect males as well as females.

This condition has therefore been called the congenital variant of RTT,[8] and recently the term FOXG1 syndrome has been introduced.[29] These patients exhibit profound motor dysfunction, and stereotypic hand movements and abnormal breathing can be present.[32] There is rarely any speech development and eye contact is poor.[32,33] Epilepsy is common although the age of onset can vary substantially.[34] They have progressive microcephaly[33,35] and MRI of the brain reveals poor myelinization and/or corpus callosum hypoplasia or agenesis.[32]

3 | MANY GENES, MANY DISORDERS

Apart from these 3 genes, there are at least 28 OMIM morbid genes (https://www.omim.org/) described in literature in which variants may cause gene disorders/syndromes with overlapping Rett-like phenotypes (Table 2).[9,10,14,36–38] Some of these genes are associated with well-known syndromes such as Pitt-Hopkins syndrome (*TCF4*, *CNTNAP2*, *NRXN1*), Cornelia de Lange syndrome (*SMC1A*), Phelan-McDermid syndrome (*SHANK3*), Kleefstra syndrome (*EHMT1*), Christianson type X-linked mental retardation syndrome (*SLC9A6*), Angelman syndrome (*UBE3A*), and Glass syndrome (*SATB2*). In addition,

TABLE 1 Summary of the clinical RTT features of the Danish Rett-like cases

Gene	*STXBP1*	*STXBP1*	*SCN2A*	*KCNB1*	*TCF4*	*SHANK3*	*SMC1A*
Gender	Female	Female	Female	Female	Female	Female	Female
Variation	c.1061G>A	c.230T>A	c.3955C>T	c.946G>A	c.1669dupC	c.2265 + 1G>A	c.3576delA
Inheritance	de novo	de novo	de novo	de novo	de novo	de novo	de novo
Head size	Microcephaly	Normal	Progressive microcephaly	Normal	Progressive microcephaly	Normal	Progressive microcephaly
Epilepsy	From birth to 6 mo	From 2 wk to 3 mo	From 17 mo	From 2 y	From 2.5 y	No	From 2.5 years
Other features					Dysmorphic features	Infections	
Diagnostic criteria for Rett syndrome							
Required diagnostic criteria							
Age for a period of regression followed by recovery or stabilization	1.5 y	None	17 mo	6 mo	None	5.5 y	2.5 y
Exclusion criteria for typical RTT	0/3	1/3	0/3	0/3	1/3	0/3	0/3
Brain injury	No	No	No	No	No	No	No
Neurometabolic disease or severe infection	No	No	No	No	No	No	No
Grossly abnormal development in first 6 mo	No	Yes	No	No	Yes	No	No
Main criteria	3/4	3/4	3/4	4/4	4/4	3/4	4/4
Hand skills	Partial loss	Impaired	Poor	Lost	Poor	Partial loss	Partial loss
Language	Lost	Never acquired	Never acquired	Never acquired	Never acquired	Partial loss	Lost
Gait	Partial loss	Impaired	Impaired	No gait	Impaired	Normal	No gait
Stereotypic hand movements	No	No	Stereotypies or automatisms	Hand wringing	Hand wringing	Hands to mouth	Hand wringing
Supportive criteria for atypical RTT	8/11	5/11	7/11	3/11	4/11	4/11	5/11
Breathing abnormality	Yes	No	Yes	Yes	Yes	No	Yes
Bruxism	Yes	Yes	Yes	No	No	Yes	No
Impaired sleep pattern	Yes	No	Yes	Yes	Yes	Yes	No
Abnormal muscle tone	Yes	Yes	Yes	Yes	Yes	No	Yes
Peripheral vasomotor disturbances	No	No	No	No	No	No	No
Scoliosis/kyphosis	Yes	Yes	No	No	No	No	Yes
Growth retardation	Yes	No	Yes	No	No	No	Yes
Small cold hands and feet	Yes	No	Yes	No	No	No	Yes
Inappropriate laughing/ screaming spells	No	No	Yes	No	Yes	Yes	No
Diminished response to pain	Yes	Yes	Yes	No	No	Yes	No
Intense eye communication	No	Yes	No	No	No	No	No
RTT diagnosis (based on the Neul criteria)	Atypical	Atypical	Atypical	Typical	RTT-like	RTT-like	Typical

The human phenotype ontology (HPO) terms corresponding to the symptoms, which are part of the Rett-syndrome diagnostic criteria are listed in Table S1.

TABLE 2 List of causative genes in Rett-like diagnoses or differential diagnoses and the phenotypical overlap with Rett syndrome

		Present in RTT										Not present in RTT			
		Required				4 main criteria				Other common symptoms		Exclusion criteria	Other symptoms		
		Developmental regression	Purposefull hand movements lost/absent	Speech severe deficit/loss	Gait abnormality	Stereotypic hand movements	Breathing abnormality	ID	Epilepsy	Microcephaly	CNS abnormality	Dysmorphic facial features	Other prominent symptoms	Disorders	OMIM#	Inheritance
RTT genes	*MECP2*	+	+	+	+	+	+	+	+	+	-	-		Rett Syndrome	312750	XLD
	CDKL5	+	+	+	+	+	+	+	+	+	-	+		Epileptic encephalopathy 2	300672	XLD
	FOXG1	+	+	+	+	+	-	+	+	+	+	-		Rett syndrome, congenital variant	613454	AD
Well-known syndrome genes	*SMC1A*	+	+	+	+	+	+	+	+	+	+	+		Cornelia de Lange syndrome 2	300590	XLD
	TCF4	-	+	+	+	+	+	+	+	+	+	+		Pitt-Hopkins syndrome	610954	AD
	CNTNAP2	+	+	+	+	+	+	+	+	+	+	+		Pitt-Hopkins like, syndrome 1	610042	AR
	NRXN1	-	+	+	+	+	+	+	+	+	+	+		Pitt-Hopkins like syndrome 2	614325	AR
	SHANK3	+	-	+	+	+	-	+	+	-	+	+		Phelan-McDermid syndrome	606232	AD
	SATB2	-	+	+	+	+	+	+	+	+	-	+	CP	Glass syndrome	612313	AD
	SLC9A6	+	-	+	+	-	-	+	+	+	+	+		Mental retardation, X-linked syndromic, Christianson type	300243	XLD
	EHMT1	+	-	+	+	-	-	+	+	+	+	-	CHD	Kleefstra syndrome	610253	AD
	UBE3A	-	-	+	+	+	-	+	+	+	+	+		Angelman syndrome	105830	AD
Genes of epilepsy	*STXBP1*	+	+	+	+	+	-	+	+	+	-	-		Epileptic encephalopathy 4	612164	AD
	SCN1A	+	+	+	+	+	-	+	+	+	-	+		Epileptic encephalopathy, early infantile, 6 (Dravet syndrome)	607208	AD
	SCN2A	+	+	+	+	+	-	+	+	+	-	-		Epileptic encephalopathy, 11	613721	AD
	SCN8A	+	-	+	+	+	-	+	+	+	-	-		Epileptic encephalopathy, 13	600702	AD
	GRIN2A	+	-	+	+	+	-	-	+	-	-	-		FESD (incl. Landau-Kleffner syndrome)	245570	AD
	GRIN2B	-	-	+	+	+	+	+	+	+	-	+		Epileptic encephalopathy, early infantile, 27	616139	AD
	HCN1	-	+	+	+	+	+	+	+	+	-	-		Epileptic encephalopathy, early infantile, 24	602780	AD
	SLC6A1	+	?	+	+	+	-	+	+	?	?	+		Myoclonic-atonic epilepsy	616421	AD
	KCNA2	+	+	+	+	-	-	+	+	+	+	+		Epileptic encephalopathy, early infantile, 32	616366	AD
	EEF1A2	-	-	+	+	+	+	+	+	+	-	+		Epileptic encephalopathy, early infantile 33	616409	AD
	KCNB1	+	+	+	+	+	-	+	+	+	-	-		Epileptic encephalopathy, early infantile, 26	616056	AD
Other genes	*WDR45*	+	+	+	+	+	-	+	+	+	+	+		Neurodegeneration with brain iron accumulation 5	300894	XLD
	ST3GAL5	+	+	+	+	+	-	+	+	+	-	+	SPD	Salt and pepper developmental regression syndrome	609056	AR
	IQSEC2	+	+	+	+	+	+	+	+	+	-	-		X-linked mental retardation, MRX1	309530	XLD
	MEF2C	-	+	+	+	+	-	+	+	-	+	+		*MEF2C* haploinsufficiency syndrome	613443	AD
	SLC35A2	-	+	+	+	+	-	+	+	+	+	+	RP	Congenital disorder of glycosylation type IIm	300896	XLD
	MFSD8	+	+	+	+	+	+	+	+	+	+	-	VL	Ceroid lipofuscinosis neuronal 7	610951	AR
	EIF2B2	+	+	+	+	+	-	+	+	+	+	-		Leukoencephalopathy with vanishing white matter	603895	AR
	ZNF238	+	-	+	+	+	+	+	-	+	+	+		Mental Retardation, autosomal dominant 22 (AD)	612337	AD

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CHD, coronary heart disease; CP, cleft palate; FESD, epilepsy, focal, with speech disorder and with or without mental retardation; SPD, skin pigmentation disorder; RP, retinitis pigmentosa; VL, visual loss; XLD, X-linked dominant. Plus (+) is noted if the symptom has been described in one or more patients with pathogenic variant in the gene. The symptoms emphasized are the main clinical features according to the 2010 classification of clinical Rett and other very specific features of RTT. Gray color are clinical symptoms in common with RTT.

a substantial number of genes are epileptic encephalopathy genes (*STXBP1*, *SCN1A*, *SCN2A*, *SCN8A*, *GRIN2A*, *GRIN2B*, *HCN1*, *SLC6A1*, *KCNA2*, *EEF1A2* and *KCNB1*).

4 | DANISH COHORT OF RTT, ATYPICAL RTT AND RETT-LIKE PHENOTYPES

In Denmark, patients with clinical features suggestive of RTT are referred to the National Danish Centre for Rett syndrome and currently, we have registered 146 living patients. All these patients were initially investigated for the 3 known RTT genes and the sequence variant distribution is: *MECP2*: 99 cases, *CDKL5*: 10 cases, and *FOXG1*: 2 cases.

Among the patients, without deficiencies in 1 of these 3 genes (n = 35), pathogenic sequence variants were identified in *SCN2A* (n = 1), *STXBP1* (n = 2) and *TCF4* (n = 1); all genes previously linked to Rett-like phenotype (Table 2), using different technologies including single gene or whole exome sequencing, and a previously described epilepsy gene panel.[39] Notably, in one patient we identified a de novo variant in *KCNB1*, which was not previously linked to Rett syndrome spectrum. Patient 2 (*STXBP1*) and patient 3 (*SCN2A*) have previously been published[40,41] (Table 1).

Remaining patients were investigated using an in-house gene panel which included the genes described in Table 2. Through this approach we identified 2 patients with variants within *SMC1A* (n = 1) and *SHANK3* (n = 1) (Table 1). With these results, pathogenic variants of a total of 23 different have been found in RTT/atypical RTT/Rett-like patients (Figure 1).

The project was approved by the Danish regional ethics committee, the regional data protection agency and informed consent was obtained from all participating patients.

5 | CLINICAL OR GENETIC DIAGNOSIS?

The description of variants within several different genes in patients with overlapping phenotypes creates practical challenges with diagnosis in clinical practice. Next generation sequencing-based methodologies (gene panels or whole exome/genome sequencing) have overcome some difficulties and diagnosis tends to move from a sole clinical to a genetic confirmation. However, understanding the clinical

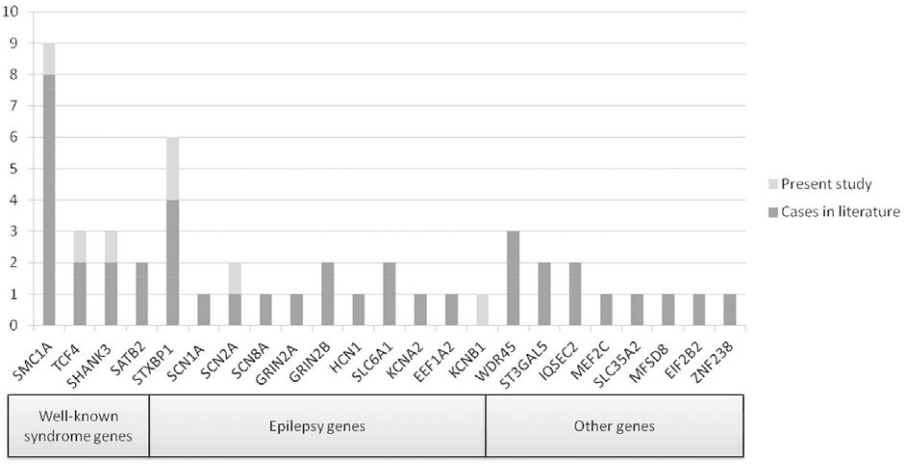

FIGURE 1 Twenty-three OMIM genes found in Rett-like phenotypes in literature (dark gray) and in the Danish database (light gray)

picture of different disorders is crucial for selection of the most relevant genes to be investigated and for assessing the clinical significance of genomic variants identified in these genes. In the following section we will compare different disorders and causative genes in comparison with RTT features (Table 2).

5.1 | Pitt-Hopkins and Pitt-Hopkins-like syndromes

Pitt-Hopkins syndrome was first described in 1978 in patients with distinct facial dysmorphism and overbreathing.[42] Neurodevelopment and speech are severely impaired, and several patients have progressive microcephaly and seizures.[28,43] Gait is often ataxic. Fetal pads on fingers and toes, and stereotypic hand movements such as hand clapping are important features. *TCF4* is the main causative gene for the classical Pitt-Hopkins phenotype;[44] variants in this gene have also been reported in 2 patients with a Rett-like phenotype.[10,12] In the Danish cohort, a single patient suspected of having RTT due to hyperventilation and hand stereotypies has a pathogenic *TCF4* variant (Table 1).

Bi-allelic loss-of-function variants in *CNTNAP2* or *NRXN1* can also result in a Pitt-Hopkins-like phenotype.[45] These patients also have severe ID and in some regression or stagnation in development.[45,46] Other prominent symptoms include epileptic seizures, a speech deficit with loss of verbal skills and hyperventilation; and some of the patients are described as being non-dysmorphic.[46] Even though variants of these genes are not yet found in Rett-like patients, they should be included in the genomic analyses of this patient group due the phenotypic overlap.

5.2 | Cornelia de Lange syndrome

CdLS is characterized by ID, a recognizable pattern of dysmorphic facial features (synophrys, thick-arched eyebrows, long eye lashes and downslanting palpebral fissures), hirsuitism, short neck, and possible presence of major malformations, such as limb defects.[47] There are 5 known genes associated with CdLS. Mutations in *SMC1A* are the second most common cause of CdLS, and commonly associated

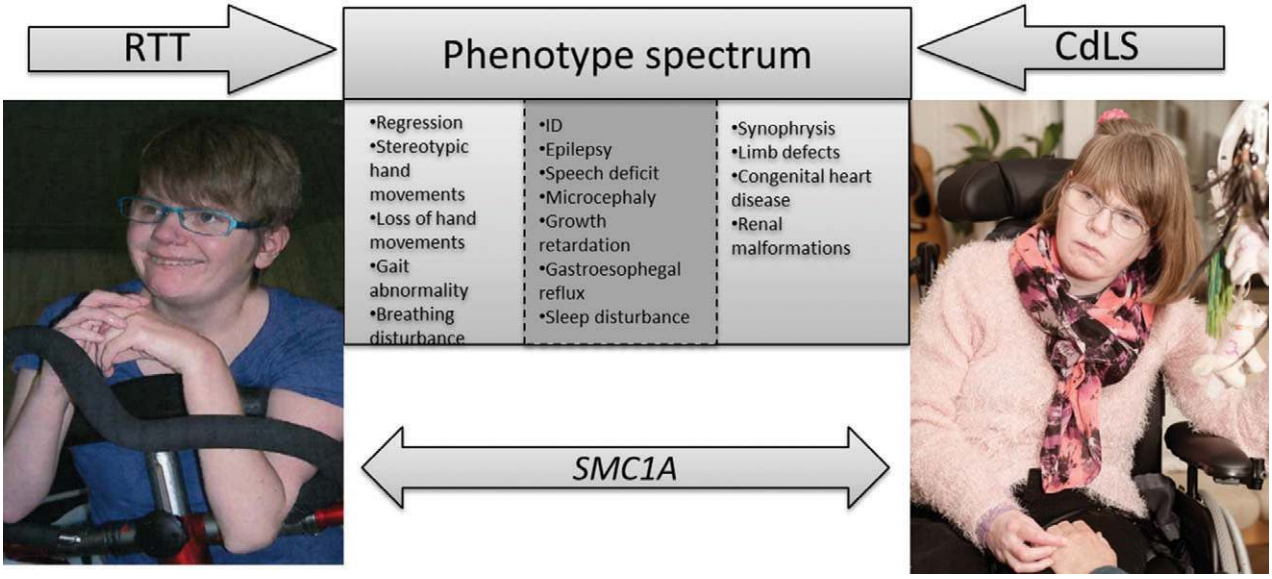

FIGURE 2 Clinical spectrum of *SMC1A* spanning from Rett syndrome to Cornelia de lange syndrome (CdLS). The photographs belong to the same patient. On the left photograph her hand wringing can be seen, but the eyebrows are covered. On the right side the synophrysis is slightly observable, but her hand movements cannot be seen as her hands are being held. In this respect she has the 2 very characteristic symptoms of both syndromes simultaneously. Photography on the right courtesy of Sofie Amalie Kloughart

with seizures, but limb defects are rare.[47] The phenotype associated with *SMC1A* variants may in some include Rett-like features[47,48] (Figure 2). They may have hand stereotypies, apnea, microcephaly, and some have a period of regression. *SMC1A* variants have been described in several patients with a Rett-like disorder,[11,49] and we identified a single patient with atypical RTT in the Danish cohort (Figure 1). The phenotypic spectrum of *SMC1A* spans from CdLS to Rett-like phenotypes, and *SMC1A* can now be considered as the fourth most common gene mutated in patients with a clinical Rett syndrome spectrum (Figure 1).

5.3 | Phelan-McDermid syndrome and *SHANK3*

Phelan-McDermid syndrome patients have various degrees of ID and speech deficits, epilepsy, hypotonia, structural brain and/or renal abnormalities and prevalent dysmorphic features, including a pointed chin and dysplastic toe nails.[50,51] The syndrome is caused by microdeletions encompassing *SHANK3* at 22q13 or a pathogenic variant in this gene, which is also associated with autism.[52] *SHANK3* variants have been reported in 2 patients with RTT[53] and a Rett-like phenotype,[12] respectively. In the Danish cohort a *SHANK3* variant was identified in a single patient, who fulfills some of the main criteria of RTT, but due to her normal gait, not categorized as typical RTT. On the other hand, she has classical autistic behavior compatible with a *SHANK3* variant.[52]

5.4 | Christianson type X-linked mental retardation

Christianson type X-linked mental retardation syndrome was first described in 1999 in a large family with males affected with profound ID, absence of speech and epilepsy.[54] Since then, several patients with common features (such as ataxic gait, hyperkinetic movements, a happy demeanor and poor fine motor skills) have been reported.[55,56] Epilepsy is reported in approximately 80% of cases, and some had a period of regression.[55,56] Because of this combination of clinical features, the syndrome has been considered a differential diagnosis of Angelman syndrome.[57] Christianson type X-linked mental retardation is caused by pathogenic variants in *SLC9A6* and has also been identified in 2 Rett-like patients.[11,12]

5.5 | *SATB2*-associated syndrome (Glass syndrome)

Pathogenic variants in *SATB2* have been identified in patients with neurodevelopmental disability, speech deficits and non-specific dysmorphic features, which together have been named as Glass syndrome or "*SATB2*-associated syndrome." Many patients have cleft palate or dental anomalies, but seizures were not prominent and they do not exhibit neurodevelopmental regression.[58,59] *SATB2* variants have also been described in 2 patients with a Rett-like phenotype, both of whom had hand stereotypies, impaired hand function and ID, but had no period of regression or seizures.[37] *SATB2*-associated syndrome should be considered when evaluating Rett-like patients, especially if they have oral anomalies.

5.6 | Kleefstra syndrome

The key features of Kleefstra syndrome are ID, hypotonia, dysmorphic features and cardiac defects.[36,60] However, some characteristic symptoms overlapping with RTT, such as speech loss and impaired walking, may be present.[61] Additional non-specific RTT features, including microcephaly, a sleep disorder and teeth grinding, have been described numerously.[60] Some patients have stereotypic movements and respiratory abnormalities, but are different to those observed in RTT patients.[36,61] Kleefstra syndrome is caused by 9q34.3 microdeletions including *EHMT1* or sequence variants of this gene.[60] *EHMT1* variants have not yet been reported in patients with a Rett-like phenotype, but have great phenotypic overlap and has been linked to the Rett-like spectrum.[36]

5.7 | Angelman syndrome

Angelman syndrome (AS) and RTT have often been described as potential differential diagnoses of each other, because they both present with severe ID, microcephaly, speech deficits and abnormal hand movements.[36] However, there are clinically identifiable differences between AS and RTT: AS patients have facial dysmorphism and they do not have hand wringing, but hand flapping. The EEG is almost always abnormal and often with a classical AS pattern.[35] AS can be caused by several genetic/epigenetic mechanisms, including variations in *UBE3A*,[62] variants of which have not yet been reported in Rett syndrome patients.

5.8 | Epilepsy

More than 500 genes have been associated with epilepsy, including genes causing encephalopathy, and pathogenic variants of several of the latter have also been described in patients with Rett-like features (Table 2, Figure 1). In Figure 3, we have compiled the age of onset of seizures for all the genes that have been associated with RTT or Rett-like clinical spectrum, as the type and age of onset of epilepsy can be an important indicator of which group of genes is probably to be causative. The epileptic encephalopathies may overlap with Rett-like phenotypes, especially where there is a period of regression with the onset of epilepsy, together with progressive microcephaly, and intellectual, speech and motor deficits.[14] Epileptic encephalopathies are defined as conditions where the progressive disturbance in cerebral function is thought to be the result of the epileptiform abnormalities.[63] However, in some of the so-called epileptic encephalopathies it is probably that the neurodevelopmental co-morbidities are primary, because neurodevelopmental abnormalities can occur before the onset of seizures, and in fact some patients never experience any seizures. This has been the case with *STXBP1* variants, for instance, where patients have moderate to severe ID, speech deficits, ataxia and tremor[64–66]; epilepsy is described in 95% of cases with a median age of 6 weeks but ranging from 1 day to 12 years.[65] Six patients with a Rett-like phenotype, including 2 Danish patients, have been found to have *STXBP1* variants[10,11,14,67] (Figure 1).

Variants in *SCN1A*, *SCN2A* and *SCN8A* lead to early onset of seizures and variants in these genes have been described in single cases with Rett-like features. The development of epilepsy is variable in

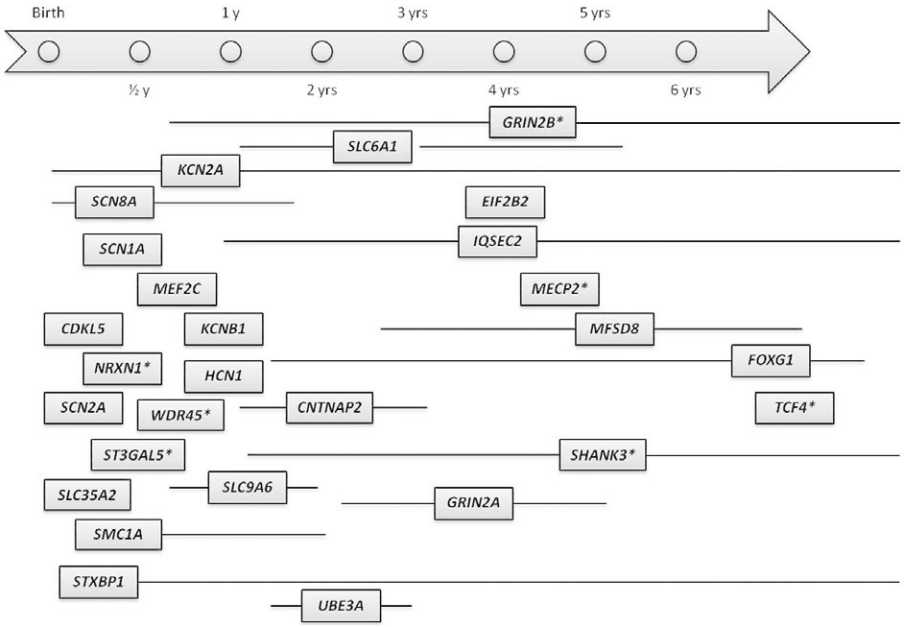

FIGURE 3 Average time for first epileptic seizure.* indicates that >5% of patients with variations in this gene have been reported without epilepsy

these cases, but in all of them a period of regression has followed the epileptic seizures.[12,14,68] In addition, patients may have ataxia, encephalopathy, various degrees of ID and hand stereotypies, and so these genes should be considered in Rett-like patients with early onset epilepsy. The severity of epilepsy is variable in patients with *SCN1A*, and an *SCN1A* variant was found in 1 patient with a Rett-like phenotype.[12] In the Danish cohort we identified a single patient with an *SCN2A* variant. She was referred with the suspicion of RTT, but her clinical history was more suggestive of a primary epileptic encephalopathy disorder, because the regression was related to the onset of intractable epilepsy.

GRIN2A and *GRIN2B* are 2 genes which cause ID and childhood onset epilepsy.[69] Variants in *GRIN2A* cause a clinical heterogeneous disorder, and have been reported in 20% of patients with Landau-Kleffner syndrome, continuous spike and waves during slow-wave sleep syndrome and electroclinically atypical rolandic epilepsy.[70] *GRIN2B* is currently considered an epileptic encephalopathy gene,[71,72] but variants have been reported in patients both with and without epilepsy. Evaluation of larger cohorts is needed to better define the phenotype associated with variants in this gene. Notably, variations in *GRIN2A* and *GRIN2B* have been reported in 3 Rett-like patients, all of whom had hand stereotypies, whereas the patient with a *GRIN2B* variant also had a breathing disturbance.[11,12]

Variants of *HCN1* and *SLC6A1* have been reported only in few patients in epileptic encephalopathy cohorts[73,74]; and *EEF1A2* variants were detected in a few patients with ID, dysmorphic facial features epilepsy with a variable age of onset.[75] Variants in these genes are described in single patients with a Rett-like phenotype, including stereotypic hand movements and breathing abnormalities as distinct features of RTT.[11,12]

KCNA2 variants are phenotypically linked to infantile epilepsy and episodic ataxia,[9] but also to hereditary spastic paraplegia.[76] The only Rett-like phenotype patient with a *KCNA2* variant had an onset of regression a few months before the onset of intractable epilepsy. She also had loss of hand skills, hand stereotypies, microcephaly and a speech deficit.[9]

KCNB1 has previously been described as a gene related to epileptic encephalopathy and ID, and sequence variants have only been described in a few patients, one of whom had handwringing.[77,78] *KCNB1* variants have not been previously described in Rett-like patients, even though they may be associated with clinical features overlapping with those of RTT. In the Danish cohort we identified a single case with pathogenic *KCNB1* variant. The patient displayed many RTT features, including neurodevelopmental regression, loss of hand function, hand stereotypies and a speech deficit, and the onset of cognitive and motor decline was prior to her seizures. We suggest that this finding warrants the inclusion of *KCBN1* in the expanding group of Rett-like genes.

5.9 | *WDR45* and other genes

WDR45 variants were first linked to a neurodegenerative disorder with iron deposits, and have been reported in 4 patients with an initial diagnosis of RTT or a Rett-like disorder, mainly because of cognitive and motor decline and hand stereotypies. Patients with *WDR45* variants can be interpreted as Rett-like in the early stages of development before the brain MRI scans displaying the iron deposits typical of WDR45 disorder become obvious.[11,79]

Variants of all the other genes listed in Figure 1,[10,37,80–82] except for *WDR45*,[38,79,83] have been observed in only 1 or 2 patients, and these genes are described in more detail in Appendix S1 (Supporting information).

6 | CLINICAL SIGNATURES OF RETT-LIKE PHENOTYPES

In a cohort of 35 Danish patients with Rett-like features but without *MECP2*, *CDKL5* or *FOXG1* variants, 6 patients revealed pathogenic changes in 5 other genes (*SMC1A*, *TCF4*, *SHANK3*, *STXBP1* and *SCN2A*), previously linked to a Rett-like phenotype. Furthermore, we

identified a *KCNB1* variant, expanding the range of "Rett spectrum genes."

These findings, together with the published reports, underscore that RTT and Rett-like phenotypes represent a clinically heterogeneous group of disorders, which may be designated as being part of a Rett syndrome spectrum (Figure 1). The underlying genetic defects are also quite heterogeneous, with pathogenic variants reported in a number of genes, but where variants of each gene are detected in only a few patients, as outlined above. However, a number of recurrences have been reported in a number of genes such as *SMC1A*, *TCF4*, *SHANK3* and *WDR45*, as well as a group of epileptic encephalopathy genes, all of which should be considered in the molecular diagnosis of patients with Rett-like phenotypes.

The reports of Andreas Rett and Bengt Hagberg and international colleagues, who undertook thorough initial evaluations of patients with RTT, unique co-morbidities have been identified.[16] These co-morbidities distinguish patients with RTT from those who have other neurodevelopmental disorders. Some of the recent genes associated with Rett-like phenotypes were detected through a genotype first approach as a consequence of large-scale genetic screening technologies, but not based on the clinical phenotype of the patients. However, it is possible to describe co-morbidities when patients are extensively phenotyped and compared with an adequate cohort of cases with mutations in the same gene. Descriptions of genes in a specific group of patients with a single major clinical feature like epilepsy may not emphasize other features or co-morbidities. Therefore, the full spectrum of the clinical picture will only be revealed when larger cohorts of patients with pathogenic variants of the same gene are described. This can lead to the "lumper" and "splitter" conundrum, where, for instance, newly identified genes associated with a Rett-like phenotype and severe epilepsy may be perceived as primary epileptic encephalopathies, or may be perhaps cast as separate syndromes based on their spectrum of co-morbidities. This has been discussed especially with regards to *STXBP1* variants[65,84] that have been recurrently reported in Rett-like patients (Figure 1). We also suggest a new "Rett-like gene," namely *KCNB1*, where several patients harboring mutations in this gene have handwringing and regression.

In the Danish cohort we found that using the clinical criteria described by Neul et al, the diagnosis of RTT is often very clear and pinpoints to a phenotype associated with *MECP2* variants with great accuracy.[23] However, it can be argued if the atypical RTT criteria really apply to patients with variants in *CDKL5* and *FOXG1*, because these patients often have early neurodevelopmental symptoms and/or early onset epilepsy. We find that when diagnosing Rett-like patients it is helpful to establish the age of onset of epilepsy as a pointer to the correct molecular diagnosis (Figure 3). In the Danish cohort, a female patient was molecularly diagnosed, at the age of 52, with a *CDKL5* variant by direct sequencing, which was performed because clinical examination and a thorough medical history revealed a period of severe epilepsy in early infancy. Thus, it should always be remembered that the phenotype may evolve with time. However, one must be cautious about applying hard and definite rules. For instance, for *FOXG1* the mean age of onset of seizures has been reported as 6.8 years, but seizures can occur as early as 6 months of age, and not all of the patients have seizures (87%).[34] Thus, a variant in this gene may be considered if there are other features suggestive of a *FOXG1* defect, regardless age of onset of seizures (Figure 3).

When evaluating a patient who does not fulfill the clinical RTT criteria but has overlapping features, some key features should be taken into consideration in order to establish the diagnosis: psychomotor development should be carefully assessed for the first year of life to evaluate the age of onset of regression and the age of onset of epilepsy. Furthermore, careful characterization of hand movements and breathing pattern are invaluable. Because of the clinical and genetic heterogeneity, the diagnostic approach for patients with a Rett-like phenotype is shifting to a genotype first approach using gene panels, whole exome or genome sequencing. Nevertheless the clinical evaluation with identification of distinct clinical features is still highly crucial to assess the validity of causation of the putative sequence variants. Furthermore, as more patients with variants in the same genes are identified, clinical subgroups can be outlined.

7 | PERSPECTIVES

From a clinical perspective an overview of the genes involved in typical RTT, atypical RTT and Rett-like phenotypes enables a better understanding of the genetic landscape of the RTT spectrum. From a research perspective, the genes associated with Rett-like phenotypes need to be elucidated further in order to gain a more complete understanding of the genetic and functional networks involved. Apart from the known genes, variants in a number of other genes with yet unknown functions have been found through screening of large Rett-like phenotype cohorts.[10,12] Some of these may represent new candidate genes and further investigations of future cohorts and functional studies are necessary to establish their potential role in this disease pathogenesis. Furthermore, elucidation of the functional pathways involved could pave the way for the development of future targeted therapies.

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Conflict of interest

The authors declare no conflict of interests.

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SUPPORTING INFORMATION

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