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ORIGINAL ARTICLE

Monogenic disorders that mimic the phenotype of Rett syndrome

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Abstract

Rett syndrome (RTT) is caused by mutations in methyl-CpG-binding protein 2 (*MECP2*), but defects in a handful of other genes (e.g., *CDKL5*, *FOXG1*, *MEF2C*) can lead to presentations that resemble, but do not completely mirror, classical RTT. In this study, we attempted to identify other monogenic disorders that share features with RTT. We performed a retrospective chart review on $n = 319$ patients who had undergone clinical whole exome sequencing (WES) for further etiological evaluation of neurodevelopmental diagnoses that remained unexplained despite extensive prior workup. From this group, we characterized those who (1) possessed features that were compatible with RTT based on clinical judgment, (2) subsequently underwent *MECP2* sequencing and/or *MECP2* deletion/duplication analysis with negative results, and (3) ultimately arrived at a diagnosis other than RTT with WES. $n = 7$ patients had clinical features overlapping RTT with negative *MECP2* analysis but positive WES providing a diagnosis. These seven patients collectively possessed pathogenic variants in six different genes: two in *KCNB1* and one each in *FOXG1*, *IQSEC2*, *MEIS2*, *TCF4*, and *WDR45*. $n = 2$ (both with *KCNB1* variants) fulfilled criteria for atypical RTT. RTT-associated features included the following: loss of hand or language skills ($n = 3$; *IQSEC2*, *KCNB1* x 2); disrupted sleep ($n = 4$; *KNCB1*, *MEIS2*, *TCF4*, *WDR45*); stereotyped hand movements ($n = 5$; *FOXG1*, *KNCB1* x 2, *MEIS2*, *TCF4*); bruxism ($n = 3$; *KCNB1* x 2; *TCF4*); and hypotonia ($n = 7$). Clinically based diagnoses can be misleading, evident by the increasing number of genetic conditions associated with features of RTT with negative *MECP2* mutations.

Keywords Rett syndrome · Mendelian disorders · Mimics

Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder characterized by a wide range of neurological impairments. Affected patients often present with acquired microcephaly, epilepsy, regression in language and hand use, motor stereotypies, and apraxic gait [1]. Other features include intellectual disability (ID), autism spectrum disorder (ASD), anxiety, Parkinsonism, sleep disturbance, respiratory abnormalities, gastrointestinal issues, scoliosis, and autonomic dysfunction [2].

The first descriptions of RTT were clinical and delineated classic and atypical/variant forms of the disease. In 2010, a panel convened and revised these descriptions, establishing a unified set of diagnostic standards based on the presence or absence of certain main, exclusion, and supportive criteria. According to these consensus guidelines, both classic and atypical forms of the disease must involve regression followed by a period of recovery/stability. While classic RTT has to fulfill all of the main criteria and none of the exclusion criteria, atypical RTT needs to satisfy at least two out of four main criteria as well as five out of 11 supportive criteria [3].

Despite uniformity established by clinical criteria, a number of genes are implicated in the presentations of classic or atypical RTT. The most common cause of classic RTT is a de novo mutation in the X-linked gene *MECP2* (methyl-CpG-binding protein 2) [4]. *MECP2* encodes a transcription factor implicated in a number of regulatory processes in the brain

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important for neuronal development and growth [5]. Over time, researchers have identified other causes of RTT besides *MECP2* mutations, including defects in *CDKL5* (cyclin-dependent kinase-like 5), *FOXG1* (forkhead box G1), and *MEF2C* (myocyte-specific enhancer factor 2C) [6].

The advent of next-generation sequencing has ushered in the discovery of other causes of Rett-like presentations in patients without *MECP2* defects [6]. In one study that evaluated 21 females with features of RTT, two thirds of the patients had pathogenic variants in genes other than *MECP2*, *CDKL5*, and *FOXG1* [7]. In another study of 19 patients with features of RTT, two had pathogenic genomic imbalances, six had variants in genes already associated with neurodevelopmental disorders, and five had variants in candidate disease genes [8].

In this study, our goal was to continue to expand the genetic landscape of Mendelian disorders that share features with RTT. To this end, we performed a retrospective analysis of patients in the Kennedy Krieger Institute Neurogenetics Clinic whose features of RTT prompted *MECP2* sequencing followed by whole exome sequencing (WES) when *MECP2* sequencing was non-diagnostic. We characterized the clinical and molecular findings of these patients with features of RTT but a genetic diagnosis other than an *MECP2* defect.

Methods

Overview

We performed a retrospective chart review on $n = 319$ patients who had clinical WES for etiological evaluation of neurodevelopmental diagnoses that remained unexplained despite extensive prior workup. These disorders included intellectual disability (ID), autism spectrum disorder, cerebral palsy-like motor encephalopathy, and epilepsy. We characterized those who (1) possessed features consistent with RTT based on clinician judgment, (2) subsequently underwent *MECP2* sequencing with or without deletion/duplication analysis which was negative, and (3) ultimately arrived at a diagnosis other than RTT with WES.

Specifically, we identified every patient at our institution who underwent clinical WES for explained neurodevelopmental diagnoses, between the years 2012 and 2015, based on our internal tracking of this data. For each patient who had undergone WES, with a result that was deemed to be causative of the patient's presentation (i.e., possessing a pathogenic or likely pathogenic variant in a gene that would explain the patient's phenotype), we evaluated all clinical documentation (clinic notes as well as biochemical, molecular, and cytogenetic testing) related to etiological evaluation. We then selected out those individuals who not only had a positive result on WES but who, prior to WES, had undergone *MECP2* sequencing (with or without deletion/duplication analysis) which was negative. We further reviewed clinical notes to determine the rationale of the clinician in sending *MECP2* sequencing. We have summarized the constellation of clinical features for each patient that led to *MECP2* sequencing (see Table 1).

The Institution Review Board of the Johns Hopkins University School of Medicine approved this study under an IRB exemption protocol (IRB00098913).

Whole exome sequencing

Each patient had clinical WES performed through Ambry Genetics Laboratory (Aliso Viejo, California) or GeneDx Laboratory (Gaithersburg, Maryland). We obtained samples from the patient, parents, and any affected siblings, if applicable/available. Each laboratory performed exome sequencing and data analysis using its own bioinformatics pipeline and confirmed results with Sanger sequencing. Full details are available in a prior report [9].

Results

Molecular findings

There were seven patients with clinical features overlapping RTT who had negative *MECP2* sequencing but diagnostic findings on WES (Table 2). These seven patients collectively possessed pathogenic variants in six different genes. Two individuals had pathogenic variants in *KCNB1*; the remaining five individuals possessed pathogenic variants in the following genes: *FOXG1*, *IQSEC2*, *MEIS2*, *TCF4*, and *WDR45*.

Clinical findings

Of the seven patients, two (patients 1 and 4) met diagnostic criteria for atypical RTT and both had *KCNB1* variants (Table 3). These two patients presented with regression affecting language or hand use, stereotyped hand movements, bruxism, intense eye communication, and abnormal muscle tone.

With respect to major RTT criteria, stereotyped hand movements were present in 5/7 patients (*FOXG1*, *KCNB1* x 2, *MEIS2*, *TCF4*), and dyspraxic/absent gait was present in 3/7 patients (*FOXG1*, *KCNB1*, *WDR45*). With respect to minor RTT criteria, the four most common features were abnormal muscle tone (7/7 patients), impaired sleep pattern (4/7 patients; *KCNB1*, *MEIS2*, *TCF4*, *WDR45*), bruxism while awake (3/7 patients; *KCNB1* x 2, *TCF4*), and intense eye communication (3/7 patients; *KCNB1* x 2, *MEIS2*).

Table 1 Clinical findings of the seven patients in our cohort that led to *MECP2* sequencing, with certain features highlighted for each patient that raised particular suspicion

Patient	Features
1	Male, ID, intractable epilepsy, **stereotyped hand movements, loss of purposeful hand use**, hypotonia
2	**Female**, ID, epilepsy, **microcephaly**, hypotonia, spasticity
3	Male, ID, epilepsy, **postnatal microcephaly, hand-wringing**
4	**Female**, ID, intractable epilepsy, **hand-wringing**, bruxism
5	**Female**, ID, **autism**, epilepsy, hypotonia
6	Male, ID, autism, **hyperventilation**, bruxism, hand to mouth stereotypies, **hand-wringing**
7	**Female**, ID, **language regression**, hypotonia

Discussion

In this report, we presented seven patients with clinical features of RTT, whose *MECP2* testing was negative and who were eventually diagnosed by WES. Two of the patients met diagnostic criteria for atypical RTT, and all but one of the patients had four or more major or minor diagnostic features.

Our work adds to the growing body of literature implicating a number of different genes in RTT-like presentations, especially with the advance of next-generation sequencing. In one study of 21 girls with features of RTT, WES was able to identify pathogenic variants in different genes in two thirds of the cohort. Some of these variants affected genes previously associated with neurodevelopmental phenotypes, such as *HCN1*, *SCN1A*, *TCF4*, *GRIN2B*, and *SLC6A1*, while others were in candidate genes not previously associated with neurodevelopmental disorders, such as *SEMA6B* [7]. In another study of 22 patients with RTT, who had prior negative clinical testing for mutations in *MECP2*, *CDKL5*, and *FOXG1*, WES revealed likely pathogenic variants in the majority of cases, including in *IQSEC2*, *TCF4*, and *WDR45* [10], three of the genes identified in our cohort. In addition to these cohort studies, there have been numerous WES-based case reports implicating a variety of genes in RTT-like phenotypes, such as *SATB2* [11], *ST3GAL5* [12], and *TBL1XR1* [13].

Collectively, the molecular abnormalities in our cohort were present in genes with differing roles. These genes encode transcription factors (*FOXG1*, *MEIS2*, *TCF4*), nucleotide exchange factors (*IQSEC2*), ion channel subunits (*KCNB1*), and scaffolding proteins (*WDR45*). The diverse functioning of these genes underscores the point that different gene defects can converge onto final common pathways, leading to similar clinical phenotypes.

FOXG1

FOXG1 (forkhead box G1) belongs to a family of transcription factors containing a DNA-binding domain known as the forkhead box [14]. In humans, *FOXG1* mutations are associated with structural brain defects and severe neurological abnormalities. Affected patients have evidence of microcephaly, cerebral atrophy, gyral simplification, hypomyelination, and a thin corpus callosum [15]. Clinical features include severe ID with poor language development, epilepsy, autistic features, and mixed movement disorders [16]. Many of these clinical characteristics are also seen in RTT. In fact, researchers identified pathogenic *FOXG1* variants in patients with early onset (atypical) RTT [17] and these variants have been increasingly identified in patients with RTT [18]. Correspondingly, patient 3 in our cohort with a *FOXG1* mutation presented with postnatal microcephaly, profound ID, tonic-clonic seizures, choreoathetoid movements, hand-wringing, and scoliosis, prompting search for an *MECP2* mutation.

IQSEC2

There are multiple reports of patients with variants in *IQSEC2* (*IQ motif and Sec7 domain 2*), encoding a guanine nucleotide exchange factor for the ADP ribosylation factor (ARF) family, that present with clinical features of RTT. One such report describes a female with delayed myelination, developmental regression not affecting hand use, and hand stereotypies. She

Table 2 Molecular findings of the seven patients in our cohort with features of RTT, negative *MECP2* sequencing, and a positive diagnosis on WES

Gene	Patient 1 (male) *KCNB1*	Patient 2 (female) *WDR45*	Patient 3 (male) *FOXG1*	Patient 4 (female) *KCNB1*	Patient 5 (female) *MEIS2*	Patient 6 (male) *TCF4*	Patient 7 (female) *IQSEC2*
cDNA change	c.1135G>A	c.551delC	c.460dupG	c.1121C>T	c.955A>G	c.759C>G	c.2983C>T
Protein change	p.G379R	p.S184LfsX13	p.E154GfsX301	p.T374I	p.R319G	p.S253R	p.R995W
Zygosity	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous
Inheritance	De novo	De Novo	Presumed germline mosaicism[a]	De novo	De novo	De novo	De novo
Disease inheritance pattern	Autosomal dominant	X-linked	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	X-linked

[a] Patient has a sister with a similar phenotype who possesses the same variant

Table 3 Clinical findings of the seven patients in our cohort with features of RTT, negative *MECP2* sequencing, and a positive diagnosis on WES

Feature	Patient number Affected gene	1 *KCNB1*	2 *WDR45*	3 *FOXG1*	4 *KCNB1*	5 *MEIS2*	6 *TCF4*	7 *IQSEC2*
RTT clinical criteria								
Classification		Atypical RTT	Some RTT features	Some RTT features	Atypical RTT	Some RTT features	Some RTT features	Some RTT features
Number of major criteria		2	1	2	3	1	1	1
Number of supportive criteria		5	4	2	7	3	6	1
Growth								
>Growth retardation		−	−	−	−	−	+	−
Microcephaly		−	+	+	+	−	−	−
Cognitive								
*Loss of acquired purposeful hand skills		+	−	−	−	−	−	−
*Loss of acquired spoken language		−	−	−	+	−	−	+
Intellectual disability		+	+	+	+	+	+	+
Seizures/sleep								
Seizures		+	+	+	+	+	−	−
>Impaired sleep pattern		−	+	−	+	+	+	−
Behavioral								
*Stereotyped hand movements		+	−	+	+	+	+	−
Autism diagnosis		−	−	−	−	+	+	−
>Bruxism when awake		+	−	−	+	−	+	−
>Inappropriate laughing/screaming spells		+	+	−	−	−	−	−
>Breathing disturbances when awake		+	−	−	−	−	+	−
>Intense eye communication		+	−	−	+	+	−	−
Motor/sensory								
>Abnormal muscle tone		+	+	+	+	+	+	+
>Diminished response to pain		−	−	−	+	−	+	−
*Dyspraxic or absent gait		−	+	+	+	−	−	−
Autonomic								
>Peripheral vasomotor disturbances		−	−	−	+	−	−	−
>Small cold hands/feet		−	+	−	+	−	−	−
GI								
Constipation		+	+	+	+	−	+	−
Skeletal								
>Scoliosis/kyphosis		−	−	+	−	−	−	−

Features marked by "*" represent main clinical criteria for RTT, and features marked by ">" represent supportive criteria for atypical RTT, as delineated in [3]

had a likely pathogenic de novo *IQSEC2* frameshift deletion (c.273_282del; p.Asn91Lysfs*112). Though she did not fulfill requirements for a clinical diagnosis of typical or atypical RTT, she met 3/4 of the main criteria and 3/11 of the supportive criteria [19]. Another report mentions an *IQSEC2* nonsense mutation in a female with severe ID, developmental regression with loss of acquired language, stereotyped hand movements, and inappropriate laughing/screaming spells [20]. Patient 7 in our cohort has a relatively non-specific profile characterized by global developmental delay and hypotonia. However, consistent with other presentations of *IQSEC2*-related disorders as noted above, she did experience language regression, which was one of the features that prompted *MECP2* sequencing (Table 1).

KCNB1

Mutations in *KCNB1* (*potassium voltage-gated channel subfamily B member 1*) result in a presentation of epileptic encephalopathy characterized by multiple seizure types, ID, motor delay, and hypotonia [21]. Developmental regression can occur in early childhood [21, 22]. In some cases, patients demonstrate behavioral abnormalities, like autistic features [23], stereotyped hand-wringing [24], hyperactivity, irritability, agitation, and aggression [25]. There are no previous reports linking *KCNB1* variants to a RTT-like presentation. Both patients in our cohort with *KCBN1* mutations (patients 1 and 4) fulfilled criteria for atypical RTT. Common RTT-like features shared between them included stereotyped hand movements, bruxism when awake, intense eye communication, and abnormal muscle tone. Their presentations should raise awareness of the possibility of *KCNB1* defects as an additional cause of atypical RTT.

MEIS2

Patient 5 in our cohort has a *MEIS2* (*Meis homeobox 2*) mutation and several clinical features consistent with *MEIS2*-related disorders. Specifically, her presentation is notable for ID, ASD, minor dysmorphisms, atrial septal defect, VSD, and bifid uvula, which are features seen in *MEIS2* disruptions [26–28]. Some of her RTT-like features, including stereotyped hand movements and impaired sleep pattern, could be explained by the diagnosis of ASD. Moreover, the presence of abnormal muscle tone, which is one of the supportive criteria for atypical RTT, is relatively non-specific, and is seen in a multitude of neurodevelopmental disorders.

TCF4

Haploinsufficiency of *TCF4* (*transcription factor 4*) results in Pitt-Hopkins syndrome (PHS) [29]. PHS is characterized by ID, epilepsy, microcephaly, facial dysmorphisms, postnatal growth restriction, and intermittent hyperventilation. Episodic hyperventilation/apnea, microcephaly, and ASD-related stereotyped hand movements [30] may steer clinicians toward a diagnosis of RTT rather than PHS. In fact, patient 6 in our cohort with a *TCF4* mutation exhibited severe ID, ASD, and facial dysmorphisms. The presence of distinct facial features is more consistent with PHS and helps to distinguish PHS from RTT.

WDR45

WDR45 (*WD repeat domain 45*) mutations result in a syndrome called beta-propeller protein-associated neurodegeneration (BPAN) characterized by a spectrum of neurodevelopmental abnormalities. Global developmental delay is prominent in infancy or childhood and transforms into moderate-severe ID. Various seizure types can occur. Neurodegeneration starts during adolescence or early adulthood with the emergence of cognitive deterioration and motor abnormalities, such as dystonia, bradykinesia, and rigidity. Other characteristics of the disorder include sleep difficulties and hand stereotypies [31]. Affected patients may have features overlapping those of RTT, including developmental regression, hand-wringing, and seizures. Some may even have a diagnosis of typical or atypical RTT [31–33]. Patient 2 in our cohort (with a *WDR45* mutation) presented with epilepsy, ID, microcephaly, truncal hypotonia, appendicular spasticity, and gastrointestinal problems. The presence of microcephaly in conjunction with her other features led to *MECP2* sequencing.

Moving toward molecular definitions of disease

It may be reasonable to move away from clinical definitions of genetic disorders toward molecular or biological definitions of disorders, especially for RTT [34]. Certainly, there are benefits of defining patients by clinical descriptions, such as grouping patients with similar features for the purpose of clinical management. However, such an approach does not fare well when it comes to clinical trials for therapeutics that target disease mechanisms centered around the core genetic defect. For example, a treatment which targets neuronal maturational defects seen in *MECP2* mutations may not be effective for an ion channelopathy due to *KCNB1* alterations. Furthermore, careful neurological and behavioral phenotyping may reveal overt and subtle distinctions that confer specificities to each genetic disorder associated with RTT.

Limitations

Our work has some limitations. Notably, the patients were part of this case series because prior to pursuing WES, a clinician sent testing for *MECP2* due to some suspicion for RTT and not necessarily because the patient fulfilled diagnostic criteria for RTT. However, this approach mirrors the practice of neurologists and geneticists and acknowledges that clinical criteria exist with certain amount of leeway.

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Conflicts of interest JC is a paid consultant for Invitae, and AF is a paid consultant for Ambry Genetics and Aevi Genomic Medicine.

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