Published in final edited form as:

J Child Neurol. 2018 March ; 33(4): 286–289. doi:10.1177/0883073818754987.

An Atypical Rett Syndrome Phenotype due to a Novel Missense Mutation in CACNA1A

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Abstract

BACKGROUND—Some typical and atypical Rett Syndrome (RTT) patients lack known genetic mutations. Mutations in the P/Q type calcium channel *CACNA1A* have been implicated in epileptic encephalopathy, familial hemiplegic migraine, episodic ataxia 2, and spinocerebellar ataxia 6, but not RTT.

PATIENT DESCRIPTION—We describe a female patient with developmental regression and a de novo, likely pathogenic mutation in *CACNA1A* who meets 3 of 4 main criteria (stereotypic hand movements, loss of purposeful hand movements, gait disturbance), and 6 of 11 supportive criteria (impaired sleep, abnormal tone, vasomotor disturbance, scoliosis, growth retardation, and screaming spells) for atypical RTT. Further, she resembles the early seizure variant of RTT. Previously, three children with similar *CACNA1A* mutations have been reported, but a RTT phenotype has not been described.

CONCLUSION—*CACNA1A* mutations should be considered in children presenting with an atypical RTT phenotype, specifically, the early seizure variant.

Keywords

Epilepsy; Epileptic Encephalopathy; Genetics

Introduction

Rett Syndrome (RTT) is a disorder primarily affecting females. It is characterized by developmental stagnation and a period of neurologic regression followed by apparent

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Author Contribution

After discussing the intention and design of the case report with all fellow authors, Ms. Epperson utilized Epic and previous clinical notes to draft the initial manuscript with the assistance of Dr. Haws. Many of the clinical notes were from Dr. Gilbert. The manuscript was then critically revised by Dr. Standridge and Dr. Gilbert. All authors assisted with revisions of the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

Ms. Epperson and Dr. Haws report no conflicts of interest.

Ethical Approval

Consent for discussion of the clinical history and video of the phenomenology was provided by the family.

stabilization.[1] The RTT diagnosis is a clinical diagnosis with 97% of typical RTT patients having a *MECP2* mutation.[2] Other patients were identified that had features of the RTT phenotype but didn't meet the diagnostic requirements for typical RTT. These patients were eventually classified as atypical variants of RTT, and categories developed including an early seizure variant, a congenital variant, and a preserved speech variant.[3] A majority of individuals with the preserved speech variant have a mutation in *MECP2*. A looser association has been found between *FOXG1* and the congenital variant and *CDKL5* and the early seizure variant.[2]

Atypical RTT is characterized by meeting 2/4 main criteria and 5/11 supportive criteria with the presence of regression followed by recovery/stabilization. Main criteria include partial or complete loss of purposeful hand skills, partial or complete loss of acquired spoken language, gait abnormalities or absence of gait, and stereotypic hand movements. Eleven supportive criteria include abnormal muscle tone, scoliosis, growth retardation, inappropriate laughter/screaming spells, impaired sleep pattern, and peripheral vasomotor disturbances.[2] (See Table 1 for complete criteria). As described by Neul et. al., the early seizure variant of RTT meets the criteria of atypical RTT, but is also associated with early onset of seizures before 5 months of age, infantile spasms, and refractory epilepsy. In this report, we describe a patient with features resembling the early seizure variant of RTT possessing a novel mutation in *CACNA1A*, a gene not previously associated with RTT.

Patient Description

This 18-year-old female initially presented to Cincinnati Children's Hospital Medical Center movement disorders clinic as a second opinion at age 4 years with a presumptive diagnosis of ataxic cerebral palsy, tremors, epilepsy, and developmental delay.

The patient was born vaginally with forceps assistance at 36 weeks gestation with a weight of 2.9 kg. On her first day of life, she had a tonic-clonic seizure. An infectious work-up was negative and head imaging at 6 days of life was normal. Her seizures were initially controlled with Phenobarbital. Within the first few months of life, she was noted to have a poor sucking reflex and was unable to breast feed. By six months of age, she had decreased muscle tone and was not rolling over. At 12 months, the patient was able to sit up on her own, but crawling was never obtained. At 24–30 months, she was able to scoot on the floor. Speech was limited to babbling that began at 12 months. Throughout the patient's development, subtle signs of regression were present. For example, the patient developed the ability to bring objects to her mouth and forms of communication such as "blowing kisses" were evident, but these behaviors disappeared around 20 months.

Also at 20 months, the patient was admitted for convulsive status epilepticus during an attempt to wean phenobarbital. A transition to topiramate monotherapy also failed. Seizures have been intractable since 20 months. Subsequent anti-epileptic treatments have included phenobarbital, topiramate, valproic acid, lacosamide, levetiracetam, oxcarbazepine, carbamazepine, clonazepam, lamotrigine, zonisamide, clobazam, felbamate, ezogabine, primidone, rufinamide, vigabatrin, and a vagus nerve stimulator, with limited success in seizure control. Seizure types have included tonic, tonic-clonic, and myoclonic seizures,

some beginning with focal features like leftward eye deviation. Seizures occurred more frequently when the patient was excited, agitated, or traveling in a car. She typically had 6–10 seizures/day lasting between 10–30 seconds. Electroencephalogram recordings demonstrated extremely slow background activity with intermittent focal slowing in frontal regions. A captured seizure revealed rhythmic midline theta/alpha activity that spread to bilateral central regions with subsequent diffuse faster paroxysmal activity.

An MRI at 3 years showed mild hypomyelination, but it was otherwise normal. At 4 years, she developed persistent tremors of the trunk and extremities, titubation, severe ataxia, midline stereotypies and rocking behaviors. At this time, she was not able to ambulate or stand independently; however, she could still scoot on the floor. Her fine motor skills were overall poor, but she would reach and successfully grab toys and was able to feed herself. She did grunt and babble, but had no expressive language. She would fixate on objects briefly, but failed to maintain fixation with poor pursuit and poor eye contact. The child had intermittent episodes of agitation that led to diffuse flushing of the skin. A second MRI, performed at 5 years of age, was significant only for mild cerebellar atrophy and increased T2 signal in bilateral medial temporal lobes that was interpreted as due to recent seizures.

In the years following, the patient's course followed a pattern of subtle deterioration trailed by periods of apparent stabilization. The patient had poor weight gain particularly after 6 years of age when her weight dropped below the 1st percentile. Height growth and head circumference were similarly low with head circumference of 50 cm at 13 years of age. At this time, she was no longer scooting on the floor, had difficulty feeding herself, and experienced frequent choking. A swallow study revealed silent aspiration, and she required a gastrostomy tube. She also developed abnormal sleep patterns with erratic daytime sleepiness. Additionally, she exhibited increased agitation with frequent episodes of screaming. Most recently, scoliosis, myoclonus, dystonia, and spasticity have appeared.

Her diagnostic work-up was initially negative and included a muscle biopsy (normal aside from a slight predominance of Type I Fibers), karyotype, microarray and RTT-associated gene testing (*MECP2, CDKL5, FOXG1*). It was not until November 2016 (at 17 years of age) that next generation comprehensive sequence analysis for a panel of epilepsy associated genes revealed a likely pathogenic (see Discussion*) de novo* point mutation in the S6 transmembrane segment of domain III of the P/Q type calcium channel, *CACNA1A* (NM_001127222.1, c.2128G>A, p.Ala710Thr).

Discussion

Mutation Analysis

The *CACNA1A* gene localizes to chromosomal locus 19p13 and encodes the α-1 subunit of the neuronal P/Q-type calcium channel.[4] It falls within the 2% of most intolerant genes with the human genome.[5] Thus a very high proportion of mutations in this gene cause disease. *CACNA1A* mutations yield great phenotypic heterogeneity and can damage cortical, limbic, and cerebellar networks.[6] Previously, autosomal dominant mutations in *CACNA1A* have been associated with episodic ataxia-2 (EA2), familial hemiplegic migraine-1 (FHM1), and spinocerebellar ataxia-6 (SCA6),[4] and more recently, autism and childhood-onset epileptic

encephalopathy.[6] Specifically, nonsense mutations, deletions/insertions, and missense mutations are associated with EA2, missense mutations with FHM1, and polyglutamine expansions in the C-terminus of the alpha subunit with SCA6[4] (See Supplemental Figure 1). A consortium recently highlighted the diagnostic value of *de novo CACNA1A* mutations in contribution to epileptic encephalopathy. In the publication, five of six infants with epileptic encephalopathy found to have *CACNA1A* mutations presented with seizures on the first day of life and phenotypes similar to the current patient. Seizure type was variable but included myoclonic, tonic, tonic-clonic, and focal seizures, with multiple seizure types developing in each individual. Developmental delay, cerebral palsy with variable features, and motor features including ataxia and tremor were observed in all individuals. All 6 had missense mutations mapping to transmembrane segments.[5] The authors are not aware of novel therapeutics that have been or are being studied in animal models for *CACNA1A* patients. This is an area of potential future research.

The patient's specific mutation in the *CACNA1A* gene was found to be a novel heterozygous *de novo* missense mutation (NM_001127222.1, c.2128G>A, p.Ala710Thr) in the S6 transmembrane segment of domain III with potential impact on nearby splice sites.[7] Predictions of pathogenicity were calculated using software predictors (Table 2).[7–9] Although limitations in using software predictors exist, they are able to provide an estimation of pathogenicity that can serve as a guide for further exploration. Two of the patients with epileptic encephalopathy and *CACNA1A* mutations described previously have very similar mutations (c.2134G>A, p.Ala712Thr) to our patient. The mutation described in these patients is located two amino acids up-stream, and it causes a similar alanine to threonine transformation with potential impact on nearby splice sites. Given the similarity in phenotype amongst the two prior patients and our current patient, in addition to the software predictions regarding pathogenicity, it is likely that this novel mutation in *CACNA1A* is responsible for the observed phenotype.

Classification as an Atypical RTT Phenotype

Studies evaluating epilepsy in RTT have demonstrated that patients negative for a mutation in *MECP2* presented with earlier onset epilepsy or more severe epilepsy.[10] It has also been shown that individuals with atypical RTT have the *MECP2* mutation less frequently than individuals with the classic RTT Phenotype.[2] Likewise, atypical RTT with a severe clinical phenotype is associated with a greater prevalence of epilepsy than classical RTT.[11] These findings are consistent with the patient discussed in this report, presenting with severe, refractory epilepsy, negative for the *MECP2* mutation.

Using the most recent diagnostic criteria for RTT, this patient can be classified as having atypical or variant RTT. She experienced a period of regression followed by relative stabilization in addition to meeting 3 out of 4 main criteria (loss of purposeful hand skills, absence of gait, stereotypic hand movements) and 6 out of 11 supportive criteria (hypotonia, scoliosis, growth retardation, inappropriate screaming spells, an impaired sleep pattern, and peripheral vasomotor disturbances).[2] (See Table 1).

A study evaluating epilepsy in RTT characterized six females diagnosed with RTT presenting with the early epileptic variant, classified as presence of seizures within the first

year of life. All six lacked *MECP2* mutations, and two were found to have mutations in *CDKL5*, consistent with the findings by Neul et. al. The type of seizures varied but were inclusive of partial seizures, myoclonic, and generalized tonic-clonic. Developmental delay, deceleration of head growth, and development of hand stereotypies were noted within the group, and all six had very poor eye contact.[10] The patient in question shares many of the features depicted in this study suggesting she too exhibits the early seizure variant of RTT.

As cohorts of specific epileptic encephalopathies are established, better anti-epileptic therapies specific to each cohort can be legitimized.[3] Moreover, recognition of the *CACNA1A* mutation in addition to the *CDKL5* as a possible cause of an early epileptic variant of RTT, particularly in those with additional cerebellar signs, could help to further categorize pathogenic mutations and eventually, improve care for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the family of the proband for providing the opportunity to present this case.

Dr. Gilbert has received honoraria from the Tourette Association of America/ Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Hong Kong Society of Child Neurology and Developmental Paediatrics; has received book royalties from Elsevier and Wolters Kluwer. He has received compensation for expert testimony for the U.S. D.O.J. D.V.I.C. program. Dr. Gilbert has received research support from the NIH (NIMH, NINDS). He has received funding for work as a clinical trial site investigator from Ecopipam Pharmaceuticals (clinical trial, Tourette Syndrome) and EryDel (clinical trial, Ataxia Telangiectasia).

Dr. Standridge is on the speakers bureau and has received compensation for Lundbeck Pharmaceuticals LLC. She has received research support from rettsyndrome.org . She has also received funding for work as a clinical trial principal investigator from Neuren Pharmaceuticals (clinical trial, Rett Syndrome).

Funding

This case report was supported by NIH grant T35DK060444 and the American Academy of Neurology Medical Student Summer Research Scholarship (2017).

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Table 1

Rett Syndrome Criteria.

Rett Syndrome Criteria	
Main Criteria	
	Partial or complete loss of purposeful hand skills *
	Partial or complete loss of acquired spoken language
	Gait abnormalities: impaired or absence of ability *
	Sterotypic hand movements *
Exclusion Criteria	
	Breathing disturbances when awake
	Bruxism when awake
	Impaired sleep pattern *
	Abnormal muscle tone *
	Peripheral vasomotor disturbances *
	Scoliosis/kyphosis *
	Growth retardation *
	Small cold hands and feet
	Inappropriate laughing/screaming spells *
	Diminished response to pain
	Intense eye communication- "eye pointing"

2/4 primary criteria and 5/11 secondary criteria with presence of regression are required for the diagnosis of Atypical RTT. The criteria met in our patient are indicated with an asterix (*).

This table was adapted from Neul et. al.[2]

Table 2

Pathogenicity predictions using 4 software predictors.

Genetic Software	Prediction
MCAP	Possibly Pathogenic-95% Sensitivity MCAP Score of 0.893 (<.025 is pathogenic)
Mutation Taster	Disease Causing- Prediction Probability of >0.99
PROVEAN	Deleterious- Score of −3.66 (<−2.5 is deleterious)
SIFT	Damaging- Score of 0.001 (<0.05 is damaging)

Three of four genetic software tools predicted this specific CACNA1A mutation to be pathogenic. 1 predicted the mutation possibly pathogenic.