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Case Report

When Rett syndrome is due to genes other than *MECP2*

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Abstract. Two individuals meeting diagnostic criteria for Rett syndrome (RTT) but lacking a mutation in *MECP2*, the gene predominantly associated with this disorder, were provided additional genetic testing. This testing revealed pathogenic mutations in a gene not previously associated with RTT, *CTNNB1*, mutations in which lead to an autosomal dominant neurodevelopmental disorder affecting cell signaling and transcription factors as well as a likely pathogenic mutation in the *WDR45* gene, which is associated with developmental delay in early childhood and progressive neurodegeneration in adolescence or adulthood related to iron accumulation in the globus pallidus and substantia nigra. These two individuals are described in relation to previous reports linking multiple other genes with RTT failing to show an *MECP2* mutation. These individuals underscore the need to pursue additional molecular testing in RTT when a mutation in *MECP2* is not detected.

Keywords: Rett syndrome, *MECP2, CTNNB1, WDR45*, whole exome sequencing, gene panels

1. Introduction

Rett syndrome (RTT) is a neurodevelopmental disorder affecting young females and is typically associated with mutations in methyl-CpG-binding protein 2 (*MECP2*) [1]. In the US RTT Natural History Study (RNHS), the frequency of *MECP2* mutations has exceeded 96% in the first two cycles [2]. In the current RNHS, the frequency is nearly 98% (unpublished data). Nevertheless, as RTT is not always linked to *MECP2* mutations, diagnosis is based on meeting consensus criteria [1]. More recently, the greater application of whole exome sequencing has identified other genes in girls and women meeting these consensus criteria [3, 4]. From the US RNHS, a search of nearly two dozen individuals meeting criteria for classic or atypical RTT, revealed several mutations that have been linked to neurodevelopmental disorders [4]. Luciarello et al. have identified mutations in a similar spectrum of mutations [3]. More recently, we identified one young woman with a mutation in *CTNNB1* and a second woman with a mutation in *WDR45*. We report the clinical features of these two individuals and promote the continued search for other mutations in those who meet the clinical criteria for RTT, yet lack an identified mutation in *MECP2*.

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2. Clinical information

Participant 1 is a 15 year old female who was born at term with normal growth parameters. Parents were unrelated. During the first six months she was floppy and frequently irritable. Cognitive and motor development was delayed uniformly with slow progress until her third birthday when she had profound regression, losing pincer grasp, finger feeding, and both expressive and receptive language. She developed hand mouthing at one year and later added hand clapping and hand flapping. She had prominent drooling from 2 months, constipation at 3 years, bruxism at 4 years, and self-abuse (biting self) at 5 years. Abnormal deceleration of head growth was noted at 4 months, ultimately falling below the 2nd percentile. When evaluated at age eight, she met all consensus diagnostic criteria for classic RTT including a period of regression, the four main crtieria, and all supportive criteria except periodic breathing and intense eye-pointing [1]. Complete mutation testing for *MECP2*, including evaluation for large deletions, was normal. When seen at 15 years of age, she was alert, not vocal, and interactive, but gave eye contact for <25% of time. She had appendicular hypotonia and moderate bradykinesia, but normal strength and muscle stretch reflexes. She has dystonia at the ankles, but no tremor or other abnormal movements beyond the hand mouthing and hand clapping. She walked with a broad, dyspraxic gait. She was able to reach for a toy. She had no periodic breathing, mild scoliosis, and history of epilepsy. She demonstrated reduced response to painful stimuli. A cranial MRI was normal.

Whole exome analysis revealed a *de novo* mutation involving a c.1494dupA; p.H499Tfs*31 in the *CTNNB1* gene which had been previously associated with an autosomal dominant neurodevelopmental disorder. This mutation had not been previously identified and was not identified in ExAC, 1000 Genomes, EVS, or dbSNP. However, as a *de novo* variant (and as a type likely to cause disease), this change was predicted to be pathogenic. Mutations in this gene have been associated with microcephaly, seizures, and neurodevelopmental delay including motor and speech impairments.

Participant 2 is a 22 year old who was born at term with appropriate growth parameters. She was doing well until age 6 months when her development was noted to be slow followed by a profound regression over the next six to sixteen months. She developed little receptive language and stopped babbling and using words at 23 months, shortly after a febrile seizure. Motor skills were slow to develop and also retained longer. Grasping was lost at age 5 and unaided walking at age 14. She never ran or used stairs. When seen at age 21, she had demonstrated no deceleration of head growth, her head circumference being at the 5th percentile. She was alert and interactive most of time. She was noted to babble and to give eye contact for up to 30 seconds. She had reduced strength, but was able to sit and stand. She was able to take only a few steps with difficulty. Gait was dyspraxic on a broad-base with retropulsion. She had marked increase in tone or rigidity, dystonia at the ankles, and increased muscle stretch reflexes in the lower extremities with ankle clonus. She had constant hand-wringing/washing and finger rubbing stereotypies with picking at clothes. She was noted to exhibit bruxism while awake, difficulties swallowing, gastroesophageal reflux, constipation, and difficulties sleeping. She had no periodic breathing and demonstrated no response to painful stimuli. She was on anticonvulsant medication for seizures. She had a cranial MRI at age 8 years that was interpreted as normal.

She met all diagnostic criteria for classic RTT and had demonstrated all supportive criteria. Complete *MECP2* testing revealed a benign variant that was also present in the mother; these studies included X-chromosome inactivation assessment that was random in both the mother and daughter. Subsequent testing using an autism panel revealed a *de novo* alteration known as c.235+1G>T in the *WDR45* gene at Xp11.23. This alteration has not been previously reported but is predicted to disrupt a consensus acceptor splice site and, therefore, was classified as likely pathogenic. It also was not identified in ExAC, 1000 Genomes, EVS, or dbSNP.

3. Discussion

The question of molecular diagnosis in individuals who meet diagnostic criteria for classic or atypical RTT and who lack a pathogenic mutation in *MECP2* has been of significant interest since mutation testing was feasible for this disorder. Although previous studies have shown linkage to *CDKL5* [5–7], *FOXG1* [8–10], and *NTNG1* [11], a small number of individuals remain without a genetic causation. Recently, Luciarello et al. [3] and Sajan et al. [4] reported mutations in a number of genes associated with neurodevelopmental disorders. Luciarello et al. [3] identified mutations in 14/21 with RTT features including ***HCN1***, linked to early infantile epileptic encephalopathy; ***SCN1A***, linked to Dravet syndrome; ***TCF4***, linked to Pitt-Hopkins syndrome; ***GRIN2B***, linked to autosomal dominant cognitive impairment; and ***SLC6A1***, linked to myoclonic-atonic epilepsy and schizophrenia. Seventeen additional mutations not previously linked to neurodevelopmental disorders were also detected. Sajan et al. [4] identified mutations in 20 of 22 individuals with RTT features. In three of those, previously undetected mutations in MECP2 were found. In the remaining 17, twenty-nine intragenic mutations were identified. In 13/17, these mutations were detected in genes with known relationship to neurodevelopmental disorders. These genes were particularly linked to chromatin regulators and post-synaptic membranes. In addition to the ***TCF4*** and ***GRIN2B*** mutations noted by Luciarello et al., this study also identified mutations in ***IQSEC2***, associated with X-linked cognitive impairment; ***SMC1A***, linked to Cornelia de Lange syndrome and a RTT-like disorder; ***LAMB2***, noted in recessive Pierson syndrome; ***STXBP1***, linked to early infantile epileptic encephalopathy; ***WDR45***, associated with neurodegeneration secondary to iron accumulation; ***GRIN2A***, noted in focal epilepsy with or without cognitive impairment; and ***22q13.2-13.33*** deletion, associated with Phelan-McDermid syndrome.

The individuals reported here featured mutations, one of which had not been associated previously with RTT and one in a gene previously associated with RTT by Sajan et al. [4]. The first involved a *de novo* mutation in the *CTNNB1* gene, which codes for ß-catenin, related to cell-adhesion, cell migration, and transcription factors [12–14]. This gene is highly conserved and related to autosomal dominant neurodevelopmental difficulties including hypotonia, motor delays, and speech impairments as well as craniofacial abnormalities. In addition, Tucci et al. reported a ß–catenin mouse mutant with features similar to those identified in humans with *CTNNB1* mutations [13]. The individual associated with this disorder did not have impressive craniofacial issues, brain abnormality, or spastic diplegia but meets the other features of disorders associated with this gene (Table 1).

The second individual reported here has a *de novo* mutation in the *WDR45* gene. This mutation is similar the c.235+G>A variant previously identified as pathogenic in two other individuals [15].

Table 1
Comparison of features associated with CTNNM1 mutations and Participant 1

Features of those with CTNNB1 mutations	Participant 1
Cognitive impairment	+
Abnormal speech development	+
Hypotonia	+
Progressive spastic diplegia	–
Abnormal fine motor development	+
Microcephaly	+
Craniofacial dysmorphism	–
Abnormal brain development	–
Abnormal self-help development	+
Abnormal sleep patterns	+

Mutations in this gene have been associated with profound neurodevelopmental difficulties, sometime linked to static encephalopathy, and followed in adolescence with significant decline related to excessive iron accumulation in the globus pallidus and substantia nigra [16, 17]. This individual, although being in her early twenties, has shown no signs of rapid deterioration. However, this individual does show increased rigidity, contractures, and upper motor neuron signs consistent with RTT in later ages and the changes associated with iron accumulation.

4. Conclusion

These two individuals meeting the diagnostic criteria for RTT but lacking a mutation in *MECP*2 underscore the importance of additional genetic testing whether by whole exome screening or specific gene panels to identify the specific etiology and to direct appropriate diagnostic and therapeutic strategies related to the specific disorder identified by such testing.

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Disclosure

The authors report no disclosures.

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