



CASE REPORT

Typical Rett Syndrome in a young boy with hemizygous c.316C>T mutation in *MECP2* gene

Murat Coskun¹, Seda Erbilgin², Ibrahim Akalin³, Ilyas Kaya¹, Zeynep Nur Gulle¹, Afig Berdeli⁴

¹Istanbul University, Istanbul Faculty of Medicine, Department of Child and Adolescent Psychiatry, Istanbul - Turkey

²Istanbul Okmeydanı Training and Research Hospital, Department of Child and Adolescent Psychiatry, Istanbul - Turkey

³Istanbul Medeniyet University, Faculty of Medicine, Department of Medical Genetics, Istanbul - Turkey

⁴Ege University, Faculty of Medicine, Department of Pediatric Rheumatology, Izmir - Turkey

ABSTRACT

Mutations in the Methyl-CpG-binding protein 2 (*MECP2*) gene have been implicated in the etiology of Rett syndrome (RTT), a neurodevelopmental disorder that primarily affects girls. *MECP2* mutations in males, once thought to be lethal, are now recognized with a broad spectrum of clinical manifestations. Here we report a 3-year-old boy who presented with developmental problems and regression and eventually was diagnosed with RTT that genetic analysis revealed to be a hemizygous c.316C>T missense mutation in the *MECP2* gene suggesting somatic mosaicism with the normal 46,XY karyotype. DNA analysis of the patient's mother showed this either to be a de novo mutation or a case of gonadal mosaicism. To the best of our knowledge, this is the first case report of RTT in a young boy with a hemizygous c.316C>T mutation in the *MECP2* gene.

Keywords: c.316C>T, male, *MECP2* mutation, rett syndrome, somatic mosaicism

INTRODUCTION

Rett Syndrome (RTT, MIM 312750) is an X-linked neurodevelopmental disorder characterized by loss of spoken language and volitional hand use with the development of repetitive hand stereotypes that occur after an apparently normal initial six to eighteen months of development (1). RTT is almost exclusively seen in girls (1) and rarely reported in male patients (2-8). In 1999, Amir et al. (9) discovered that mutations in the gene encoding Methyl-CpG-binding protein 2 (*MECP2*) were associated with the most common sporadic occurrences of typical RTT in addition to rare familial cases. Mutations in *MECP2* can be detected in 95-97% of subjects with typical RTT, while a lower rate

of mutations, 50-70%, has been reported in atypical cases (1). Although the precise function of *MECP2* has not been fully understood, dysfunction or loss of *MECP2*, as observed in RTT, would be predicted to give rise to inappropriate activation of genes (10).

Typically, affected girls follow an apparently normal development during the first months of life. Between six months and two years of age, developmental regression becomes evident through the loss of speech, purposeful hand movements, and social as well as cognitive abilities (1). In the past, *MECP2* mutations in male patients have been thought to be lethal. However, today, it is supposed to present with a broad spectrum of clinical manifestations from death in infancy to developmental delay associated with seizures and

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Correspondence: Zeynep Nur Gulle, Department of Child and Adolescent Psychiatry, Istanbul Faculty of Medicine, Istanbul University, Istanbul 34390, Turkey

Phone: +90 538 625 90 60 - 212 414 20 23 **E-mail:** zeynepnur.gulle@gmail.com

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neurological disorders, as well as non-specific mental retardation (2-8,11,12). In this study, we report a 40-month-old boy who was initially diagnosed with autism at 24 months and then received the diagnosis of RTT in the 32nd month with a typical hemizygous c.316C>T mutation in MECP2 gene.

CASE

Clinical Presentation

A 24-month-old boy was referred to our hospital by his parents with a number of developmental problems and abnormal behaviors. His psychiatric examination revealed significant deficits in language and social developments, as well as several stereotypic hand movements. Despite of some level of vocalization, he almost had no meaningful words and could not understand short simple comments. Although he used to have some level of eye contact or social responsiveness in his domestic environment with family members, he made no eye contact and did not respond to his name during clinical examination. He showed almost no meaningful play or imitations. Stereotypic behaviors, such as hand clapping and wringing, were observed. He was able to walk without support. He was given a DSM-IV diagnosis of autistic disorder and referred to a special psycho-educational rehabilitation program. Laboratory workup, including inborn errors of metabolism, brain imaging, electroencephalography (EEG), and brain auditory evoked response test (BAER), were unremarkable. His parents gave verbal informed consent for the study.

Developmental History

The patient is the first child of healthy unrelated parents. He was born at term with normal spontaneous vaginal delivery after an uneventful pregnancy. His birth weight was 3200g (50 percentile), birth height was 50cm (50 percentile), and his head circumference was 34cm (25 percentile). The patient's developmental milestones included head control at the age of three months, sitting with support at the age of six months, sitting without support at the age of nine months, walking with support at the age of 12 months, and walking without support at the age of 18 months. He started to vocalize at the age of 10 months but he has acquired almost no meaningful words so far. Review of home videos revealed that, at the age of 12 months, he had developed stereotypical behaviors, such as swinging and hand clapping, and limited social responsiveness. At the age of 20 months, stereotypes such as hand

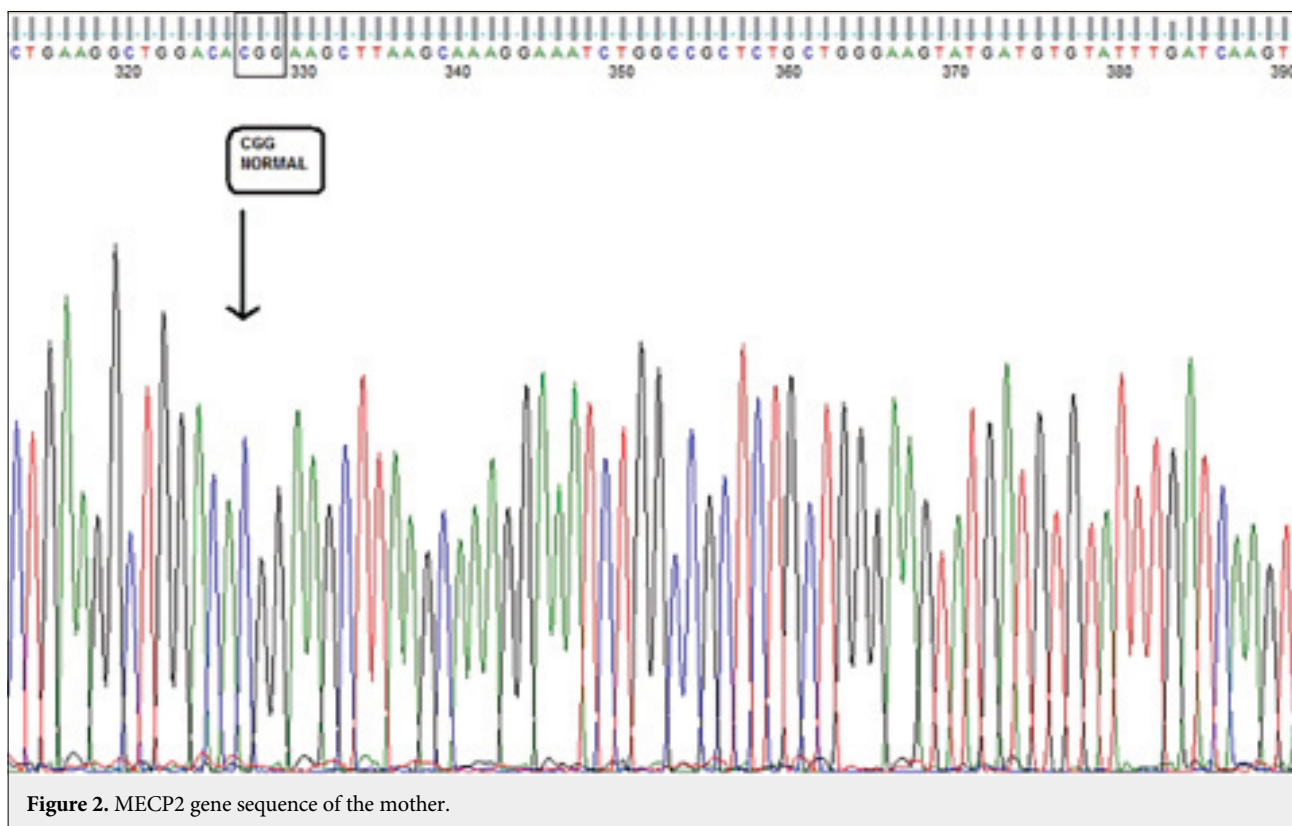
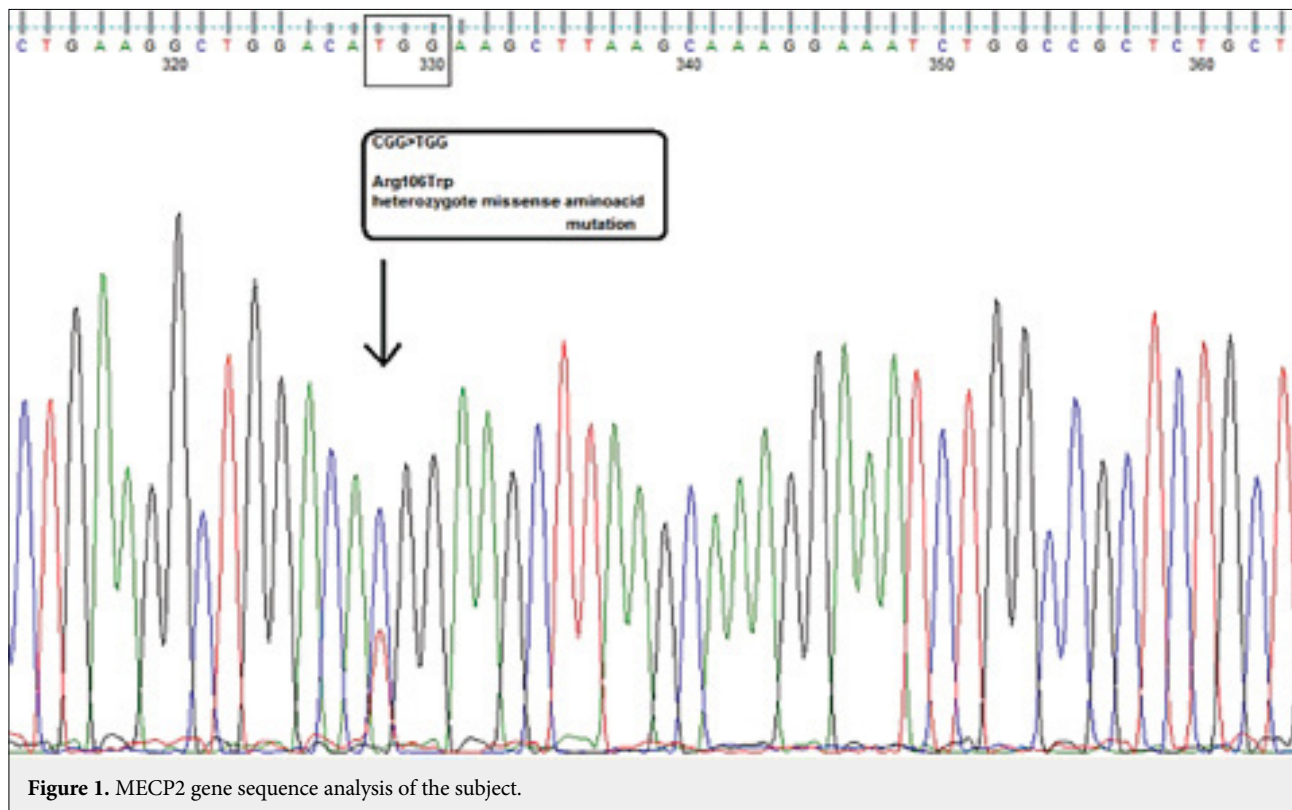
wringing and washing movements started and his purposeful use of hands and fingers began to deteriorate. He has had severe bruxism since the age of one year. His family history revealed that he has a maternal cousin with autism. No other family members had neurological diseases.

Although he attended a special education program regularly, his motor and social skills deteriorated and his stereotypic behaviors increased over time. At age 30 months, he started to show truncal ataxia and gait apraxia, and he was not able to stand up without support. His fine motor skills, such as holding a spoon in his hand, regressed. He was reported to have no eye contact or social responsiveness in the domestic environment anymore. His vocalization and bubbling also disappeared. We observed intense midline stereotypes such as hand washing and hand-to-mouth movements at the age of 30 months. He was almost always performing these midline stereotypic behaviors and it was difficult to stop this behavior with any distracters. His physical examination revealed scoliosis and mild microcephaly with a head circumference of 48cm at 30 months of age (18 percentile). Given his clinical picture, including deterioration in social and motor skills, developing intense midline stereotypic behaviors and scoliosis, a provisional diagnosis of RTT was considered. We ordered MECP2 gene mutation analysis.

Genetic Analysis

Genetic analysis was conducted for the subject and his mother using peripheral venous blood. Cytogenetic analysis of the boy revealed normal 46,XY karyotype. Molecular analyses using the MLPA (Multiplex Ligation-dependent Probe Amplification) (PO15-MECP2/Lot 0909) method did not reveal any deletion or duplication in 28 regions including MECP2, NTNG1, CDKL5, ARX, SLC6A8, L1CAM, FLNA, GDI1, and DKC1 genes. However, MECP2 (NM_004992.3, NP_004983.1) gene sequence analysis revealed a c.316C>T (rs28934907, p.R106W) hemizygous point mutation at exon three (Applied Biosystems 3130xl Genetic Analyzer, Foster City, California 94404, USA) (Figure 1). No genetic abnormality was detected in the mother (Figure 2).

After molecular genetic confirmation of RTT, the patient was followed until the age of 46 months. While he did not have clinical seizures, his sleep-deprived EEG showed diffuse slow-wave activity. Valproat 200mg/day was started by the neurologist. The patient's head circumference was 48cm at 36 months of age (10



percentile) and at 46 months of age (below the 10 percentile). At 44 months of age, he started to have occasional breath-holding spells. His problems with

gait, motor skills, stereotype behaviors, and social deficits continued with no significant change. Although his control sleep EEG was abnormal, his medication

was discontinued by the family as he had no clinical seizures.

DISCUSSION

Typical RTT with mutation in the MECP2 gene has rarely been reported in male subjects. Here we presented a male patient diagnosed with Rett Syndrome with a c.316C>T (rs28934907, p.R106W) hemizygous point mutation at exon 3 of the MECP2 gene suggesting somatic mosaicism.

While males do not develop typical Rett Syndrome unless they have a 47,XXY karyotype or somatic mosaicism, our patient revealed a clear 46,XY chromosomal constitution. Additionally, somatic mosaicism has been documented in male patients with MECP2 mutations associated with classical RTT (6,7). Therefore, we assumed our patient to be a case of somatic mosaicism for a c.316C>T mutation.

The identified mutation (p.R106W) is disease-causing since it is a missense mutation. The R106W mutation, being in a highly conservative methyl-CpG-binding domain of MeCP2, has been detected in other female patients with classical RTT (9). In-vitro studies have demonstrated that the R106W mutation within the methyl-binding domain leads to substantial deterioration of MeCP2 functions by weakening its selectivity for methylated DNA (13,14). The mutation, when transfected into cells, leads to impairment of its ability to localize to heterochromatins and in consequence to repression of transcription.

The clinical picture in male patients with confirmed MECP2 gene mutation is characterized by variable degrees of severity ranging from severe encephalopathy and early death to severe mental retardation and autistic pictures (1). In addition to typical RTT, it has been recognized that some individuals present with many of the clinical features of RTT, such as regression, but do not necessarily have all of the features of the disorder. These have been termed "variant" or "atypical" RTT (1). A literature review found several papers reporting typical or atypical Rett syndrome in male subjects with R133C (5), S134C (2), c.1158del44 or p.388X (3), c.360T>G or Y120X (6), 808C>T or R270X (7), T158M (4), and 754insC or E250X (8) mutations in the MECP2 gene. The present living case is one of the few that had typical features of Rett syndrome, where a disease-causing hemizygous c.316C>T (rs28934907, p.R106W) missense mutation at the MECP2 gene might represent somatic mosaicism. Moreover, given that the MECP2

mutations were dominant in character, the absence of a c.316C>T mutation in the mother indicated the mutation to be de novo in the patient or the presence of gonadal mosaicism in the mother (15).

Neul et al. (1) reviewed the recent diagnostic criteria and nomenclature of RTT. The possibility of RTT should be considered when postnatal deceleration of head growth is observed. Our case met all the diagnostic and exclusion criteria for typical RTT. For typical or classical RTT, in addition to a period of regression followed by recovery or stabilization, 4 main criteria should be present 1) Partial or complete loss of acquired purposeful hand skills (e.g., inability to hold a spoon), 2) Partial or complete loss of acquired spoken language (i.e. the loss of vocalization and bubbling), 3) Gait abnormalities: impaired (dyspraxic) or absence of ability (i.e. unstable and ataxic gait, inability to stand up without support), 4) Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms (incl. intense hand washing and hand to mouth movements). Two main exclusion criteria for typical RTT were also met: 1) brain injury secondary to trauma and neurometabolic disease or severe infection causing neurological problems (i.e., no significant history of trauma or neurological disorders) 2) grossly abnormal psychomotor development in the first 6 months of life (such as head control at 3 months of age, sitting with support at the age of 6 months, sitting without support at the age of 9 months, walking with support at the age of 12 months, and walking without support at the age of 18 months). Although supportive criteria are not required for a diagnosis of typical RTT, he also met several supportive criteria such as scoliosis, severe bruxism, and breath-holding spells.

The subject was initially diagnosed with autistic disorder at 24 months of age. Later on, he showed deterioration in language, social and motor skills alongside with typical midline/mouthing stereotypic movements leading to suspicion of Rett syndrome. MECP2 gene mutation analyses was requested and we found a hemizygous c.316C>T (rs28934907, p.R106W) mutation at exon three.

This case report may highlight that Rett syndrome should be considered in female and male subjects with a diagnosis of pervasive developmental disorder and genetic analysis should be recommended if they show developmental deterioration over time. Here, for the first time we reported a male subject with hemizygous c.316C>T mutation in the MECP2 gene representing

clinical features of typical Rett syndrome, suggesting somatic mosaicism.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.C., I.K.
	Literature review	S.E.
	Data analysis/Interpretation	I.A., A.B.
	Case follow-up (if applicable)	I.A., A.B., S.E.
Category 2	Drafting manuscript	M.C., Z.N.G., S.E.
	Critical revision of manuscript	I.A., A.B.
Category 3	Final approval and accountability	M.C.
Other	Technical or material support	M.C., I.A.
	Supervision	N/A

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