Cytogenetic case report

Homozygosity for MECP2 gene in a girl with classical Rett syndrome

Daniela Karall a,*, Edda Haberlandt a, Sabine Scholl-Bürgi a, Sara Baumgartner a, Montserrat Naudo b, Loreto Martorell b

a Clinical Department of Pediatrics, Medical University Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria
b Molecular Genetics Section, Hospital Sant Joan de Déu, Barcelona, Spain

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Abstract

We report a 21 year-old girl with classical Rett syndrome (RS) based on clinical diagnosis. The molecular testing of MECP2 gene revealed that the patient is homozygous for a de novo 473C > T mutation, causing the T158M amino acid change. Chromosome analysis showed a normal karyotype, and the haplotype analysis ruled out the possibility of parental disomy or microdeletion in MECP2 gene. Cultured fibroblast analysis reveals a mosaic for the mutation. This is a documented case of a homozygous female with RS.

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1. Introduction

X-chromosomal dominantly inherited Rett syndrome (RS) is a neurodevelopmental and one of the most frequent genetic diseases in girls. Clinically, phenotype spectrum is broad, ranging from primary developmental delay with inability to sit or walk and catastrophic epilepsy and only minor neurological symptoms, preserved language and well-preserved hand function [1]. Since 1999 the molecular basis is known [2,3]. De novo mutations in the coding region

* Corresponding author. Tel.: +43 512 504 23600; fax: +43 512 504 23484.
E-mail address: daniela.skladal@i-med.ac.at (D. Karall).

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of MECP2 gene have been described in a high proportion of sporadic RS patients. Nowadays, about 95% of patients with classical RS can be diagnosed genetically. However, the range of clinical manifestations has raised new questions [1,4]. We report a young woman with classical RS showing a homozygous mutation in MECP2 gene.

2. Case report

The patient is the second child of non-consanguineous Caucasian parents, her sister is healthy. After uneventful pregnancy, she was born in the 41st gestational week through Caesarean section, birth weight was 1970 g (below 3rd percentile), without signs of placental insufficiency or smoking of the mother. She spoke first words at 12th month and took first steps at 18th month. At 2 years, neurological deterioration with loss of purposeful hand skills and typical hand stereotypes started. Later, episodes of hyperventilation were observed, as well as unsteady apraxic gait. Deceleration of head growth occurred with head circumference being 45 cm (3 cm below 3rd percentile) at age 4 and 48 cm (4 cm below 3rd percentile) at age 19 years. Epilepsy was diagnosed at 4 years appearing as atypical absences, followed by a petit-mal variant 3 years later and focal epilepsy of left temporal lobe with complex focal seizures at 17 years.

With 21 years her condition is compatible with the late motor deterioration stage of RS with mental retardation, microcephaly, kyphoscoliosis, wheelchair-need and loss of perceptive and expressive language.

Brain magnetic resonance imaging at age 18 showed cerebral atrophy, magnetic resonance spectroscopy was normal. All metabolic investigations were normal. To confirm RS genetically, we tested for mutations of MECP2 gene.

3. Methods

DNA of patient and family was prepared from peripheral blood lymphocytes and patient’s fibroblasts by standard methods. The coding region of MECP2 gene was analyzed by direct sequencing, using conditions described elsewhere [2,3]. Samples from patient, parents and sister were analyzed repeatedly to exclude artefacts.

Familial segregation analysis was done using microsatellite markers based on the Génethon human genetic linkage map along the Xq28 region around MECP2 gene (data not shown). Other polymorphic markers in other chromosomes were analyzed to confirm the paternity in the family. Later, a second separate sample was requested to confirm the results obtained.

4. Results

MECP2 gene sequencing in the patient revealed the presence of a homozygous change in blood 473C > T, causing a T158M substitution (Fig. 1A), and presence of both normal and mutated alleles in cultured fibroblasts (Fig. 1B), indicating somatic mosaicism. The DNA analyses of parents and sister were normal. The normal karyogram, 46-XX, excluded possible hemizygosity. Pattern of methylation in DNA samples was normal, indicating the presence of one active and one inactive X chromosome. Normal biparental inheritance was confirmed with the polymorphic marker analysis in X chromosome (data not shown).
5. Discussion

We report a young RS woman with a homozygous mutation in MECP2 gene, this constellation has not been reported so far. The familiar haplotype rule out both the possibility of uniparental disomy and microdeletion in the gene. All the data obtained indicate a double de novo mutation in the patient, occurring at two different points in time. This event is extremely rare, but we think the underlying results allow this explanation only.

Occurrence of homozygosity (although for two mutations — R133C and R168X) was suspected for RS girls in earlier studies [5], but later proved to be a technical default caused by the primers used [6]. Recently, Li et al. [7] in their series reported two homozygous patients. However, they give no further information.

The T158M mutation is the most common found in RS, and produces an amino acid change in the methyl-binding domain of MECP2 gene [2]. These missense mutations in the methyl-binding domain are associated with less severe phenotypes than the nonsense mutations found in the transcriptional-repression domain [8]. This could be one explanation for the relatively mild clinical symptoms of this girl, similar to those of heterozygous women. The clinical picture and the survival of this patient can be explained by the existence of somatic mosaicism, as has been previously described for classical RS in girls [9,10] and in boys [11,12]. In order to

![Fig. 1. Electropherograms of the analysis of the T158M mutation. (A) Sequence analysis of blood DNA sample of the patient. (B) Sequence of DNA obtained from cultured fibroblasts. The arrow in the electropherogram indicates the point of the change.](image)
verify this possibility we analyzed MECP2 gene in cultured fibroblasts from the patient. Both the normal and the mutated alleles were seen in this sample, the results indicate somatic mosaicism for the T158M mutation, which we hypothesize is the result of an early post-zygotic mutation. In this documented case of a homozygous female patient with classical RS — not described previously in the literature, we assume that somatic mosaicism explains the patient’s survival with two copies of the same mutation.

References