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Original article

Novel non-identical *MECP2* mutations in Rett syndrome family: A rare presentation

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Abstract

Introduction: Rett syndrome (RS), an X-linked neurodevelopmental disorder and the common cause of mental retardation in females, is caused by methyl CpG binding protein 2 (*MECP2*) gene mutations with a frequency of more than 95% in classical Rett patients. Majority of RS cases are sporadic but few familial cases caused by either skewed X-chromosome inactivation in healthy female carriers or mosaicism in male carriers are also reported. Most of the times, the mutation carried in a family is the same as found in affected child.

Methods and results: Here we report a unique family carrying non-identical *MECP2* mutations in exon 2 wherein the proband with classical RS was carrying a de-novo early truncating frameshift mutation while her asymptomatic mother was carrying a missense mutation, both predicted as pathogenic mutations.

Conclusions: These findings further validate the importance of *MECP2* mutation screening in parents of all mutation positive patients and careful evaluation of the pathogenicity of the mutation found in asymptomatic carriers before providing genetic counseling to the family. The results also propose the role of other factors including other gene mutations, environmental and epigenetics factors in modifying the expression of *MECP2* mutations.

Keywords: De-novo; *MECP2*; Mosaicism; Mutation; Non-identical; Rett syndrome; SSCP; X-chromosome inactivation

1. Introduction

Rett syndrome (RS; OMIM#312750) is an X-linked neurodevelopmental disorder and the common cause of mental retardation in females [1]. RS manifest in girls with a broad spectrum of clinical phenotypes which range from classical RS phenotype to mild atypical variants [2,3]. Girls with classical RS fulfil all the essential diagnostic criteria which include a normal perinatal period followed by a period of regression, loss of acquired purposeful hand and speech skills, stereotypic hand movements, walking problems, and growth retardation [4,5]. The X-linked dominant nature of RS was thought to be lethal in males [6,7] but recent findings report male patients with a wide phenotypic heterogeneity [7]. Mutations in the methyl CpG binding protein 2 (*MECP2*) gene (OMIM#300005) which can be either point mutations or large deletion/duplications are the primary cause of RS and have been identified with a frequency of more than 95% in patients with classical RS [3,8,9].

Majority of RS cases are sporadic [10] and are caused by de-novo *MECP2* mutations but there are reports of few familial cases which are caused by either skewed

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X-chromosome inactivation (XCI) in healthy female carriers [11,12] or mosaicism in male carriers [13,14]. In majority of such familial cases the mutation is the same as found in the affected child [10,15]. We describe here a unique family in which a classical Rett female and her asymptomatic mother carry non-identical mutations in exon 2 of *MECP2* gene.

2. Subjects

2.1. Case report

A three year old girl II-4 (Fig. 1A) born to a healthy non-consanguineous couple from northern India and was referred to our hospital for neuroregression and stereotypic hand movements. Her birth was at term by normal vaginal delivery with an unremarkable perinatal and neonatal period. At the age of 16 months, her parents noticed that she was losing her acquired milestones. She stopped speaking and lost her purposeful hand skills around the age of 14 months. She was able to stand by the age of 1 year but slowly lost that ability too. She never achieved the ability to walk after this period. There was no history of seizures.

Family history was positive for unexplained death of male sibs (monozygotic twins) II-1 and II-2 (Fig. 1A) on day one of life. At the age of three, the height of proband was 82 cm, weight 9 kg and head circumference 43 cm (all <3rd percentile) by National Centre for Health Statistics standards. She had bruxism, stereotypic hand movements (mouthing), hypertonia, constipation, unexplained laughter and crying spells, poor eye contact, muscle atrophy, growth retardation and mild scoliosis. Her IQ of 25–30 on VSMS was suggestive of severe mental subnormality. Her audiometric and MRI examinations were normal. The proband was fulfilling all the essential diagnostic criteria of classical RS [4] and was enrolled for *MECP2* mutation analysis. Ethical approval was obtained from the ethics committee of our institute.

3. Methods

Blood samples were obtained after taking informed consent of parents and the DNA were extracted from peripheral blood using standard protocol. The coding region of exon 2–4 of *MECP2* gene was amplified by polymerase chain reaction (PCR) using primer sequences published in previous reports [6,8]. Two overlapping sets of primers were used to amplify exon 2 (2a, 2b) of *MECP2* gene. Single strand conformation polymorphism (SSCP) was used for mutation screening followed by bidirectional sequencing using ABI 3130 genetic analyzer (Applied Biosystems, California, USA).

The sequences were manually analyzed by visual inspection of the sequencing electropherograms using program ChromasPro version 1.33 (Technelysium Pvt. Ltd) and compared with normal *MECP2* reference sequence (GenBank: NM_004992.3). Bioinformatics softwares sorting intolerant from tolerant (http://sift.jcvi.org/) [16] and polyphen (http://genetics.bwh.harvard.edu/pph/) [17], were used for prediction of effect of mutations on the structure and function of proteins.

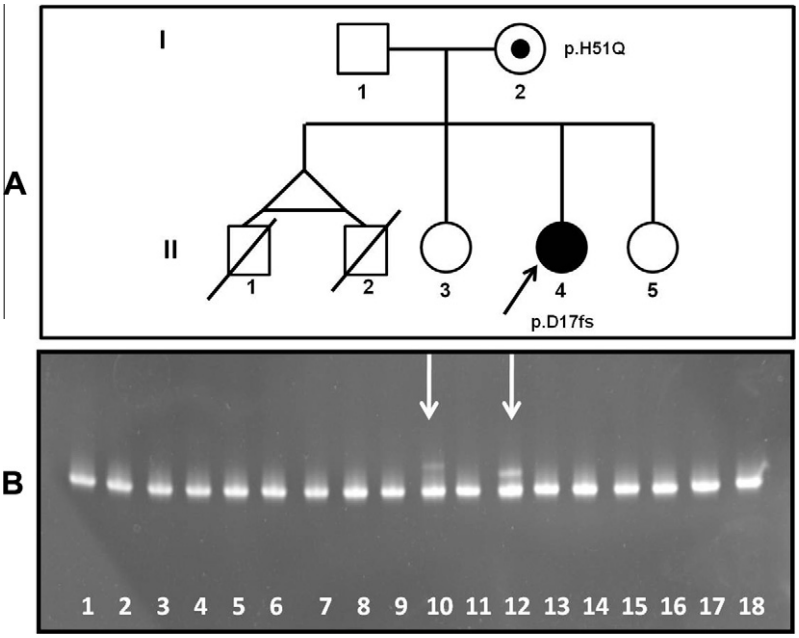

Fig. 1. (A) Pedigree of the family described in this report. The proband is indicated by an arrow. Mutations carried by the proband and her mother are given below their respective symbols. (B) Single strand conformation polymorphism gel picture showing the mobility shifts in lane 10 (proband) and lane 12 (mother of proband). Lane 11 (father) and lane 1–9, 13–18 (healthy controls) not showing any mobility shifts.