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Original article

Mutation screening of the *MECP2* gene in a large cohort of 613 fragile-X negative patients with mental retardation

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Abstract

Mental retardation affects 2 to 3% of the population and is marked by significant etiological heterogeneity, including genetic and non genetic causes. FRAXA (*FMR1*) trinucleotide expansion is widely searched in routine screening, but found in only about 2% of the patients tested. Mutations of the *MECP2* (methyl-CpG-binding protein) gene mainly cause Rett syndrome but were also shown to be involved in mental retardation. This study aimed to estimate the frequency of *MECP2* gene mutations in a large group of mentally retarded patients without FRAXA expansion. Screening by heteroduplex analysis and SSCP followed by DNA sequencing of shifted bands were performed on 613 patients, including 442 males and 171 females. Eleven sequence variants were found, including nine polymorphisms. The two others may be pathogenetic. The first one, the double nucleotide substitution c.1162_1163delinsTA leading to a premature stop codon (p.Pro388X) was found in a female patient with random X-inactivation, presenting with borderline mental impairment without any features of Rett syndrome. The second one, the c.679C>G substitution, changing a glutamine to a glutamate in the transcriptional repression functional domain (p.Gln227Glu), was found in a female patient with a moderately biased X-chromosome inactivation profile and presenting with mild intellectual delay and minor psychotic features. The low

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mutation rate suggests that a large-scale routine screening for *MECP2* in mentally retarded subjects is not cost-effective in clinical practice. Screening may be improved by a pre-selection based on clinical features that remain to be established.

Keywords: Mental retardation; MECP2; Mutation; Polymorphism; Molecular screening

1. Introduction

Mental retardation (MR) represents a public health challenge because its prevalence in the whole population was estimated to 2–3%, even if this might be slightly overestimated [25]. Variable expressivity and the large number of syndromic and non-syndromic causes of MR make it difficult to provide diagnostic precision. Careful clinical investigations of patients help in some cases to clarify the diagnosis of a given syndrome but most MR patients share a rather non specific initial presentation. Routine investigations usually include blood lymphocyte karyotype and molecular search for FRAXA trinucleotide expansion (*FMR1*). However, a FRAXA expansion, confirming the diagnosis of fragile X syndrome, is only found in about 1–2% of MR patients tested [13,29]. *MECP2* (MIM 300005) is involved in more than 90% of Rett syndrome (MIM 312750), an X-linked dominant neurodegenerative disorder occurring almost exclusively in females and *de novo* [1,6,17,43]. More recently, mutations in *CDKL5*/*STK9* have been found in Rett syndrome variants with early onset and infantile spasms [33,35,42].

A few DNA variants of *MECP2*, considered as disease causing mutations, have been found in mentally retarded males with additional clinical features related to different syndromes such as Angelman syndrome and PPM-X (X-linked pyramidal signs, parkinsonism and macroorchidism syndrome, MIM 300055) [9,19,20,27,31,41]. The most common of these mutations was the c.493C>T substitution changing an alanine to a valine (p.Ala140Val) in the methyl-CpG binding domain (MBD) [9,19,31]. The first study of *MECP2* in X-linked MR families and sporadic male patients suggested a high rate (2%) of mutations [7]. Although some of the DNA variants found in this study were later shown to be rather rare polymorphisms than disease causing mutations, *MECP2* was considered a good candidate gene for routine molecular testing in MR of unknown cause [23,28]. Previous screening studies in cohorts of male patients showed that disease causing mutations of *MECP2* has, actually, a lower incidence in MR than previously thought [21,45]. Here we report the results of a systematic search for *MECP2* mutations in large groups of males and females affected with MR and previously tested negative for the FRAXA expansion.

2. Patients and methods

2.1. Patients

We investigated 613 patients initially referred for routine FRAXA trinucleotide expansion investigations and in whom the test results were negative. Patients were recruited by medical geneticists, child neurologists, paediatricians and child psychiatrists in the various medical centres throughout the Rhône-Alpes region (Central Eastern part of France) during their daily