

# Identification of Males with Cryptic Fragile X Alleles by Methylation-Specific Quantitative Melt Analysis

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## Resumen

**BACKGROUND:** FMR1 full mutations (FMs) (CGG expansion >200) in males mosaic for a normal (<45 CGG) or gray-zone (GZ) (45-54 CGG) allele can be missed with the standard 2-step fragile X syndrome (FXS) testing protocols, largely because the first-line PCR tests showing a normal or GZ allele are not reflexed to the second-line test that can detect FM.

**METHODS:** We used methylation-specific quantitative melt analysis (MS-QMA) to determine the prevalence of cryptic FM alleles in 2 independent cohorts of male patients (994 from Chile and 2392 from Australia) referred for FXS testing from 2006 to 2013. All MS-QMA-positive cases were retested with commercial triplet primed PCR, methylation-sensitive Southern blot, and a methylation-specific EpiTYPER-based test.

**RESULTS:** All 38 FMs detected with the standard 2-step protocol were detected with MS-QMA. However, MS-QMA identified methylation mosaicism in an additional 15% and 11% of patients in the Chilean and Australian cohorts, respectively, suggesting the presence of a cryptic FM. Of these additional patients, 57% were confirmed to carry cryptic expanded alleles in blood, buccal mucosa, or saliva samples. Further confirmation was provided by identifying premutation (CGG 55-199) alleles in mothers of probands with methylation-sensitive Southern blot. Neurocognitive assessments showed that low-level mosaicism for cryptic FM alleles was associated with cognitive impairment or autism.

**CONCLUSIONS:** A substantial number of mosaic FM males who have cognitive impairment or autism are not diagnosed with the currently recommended 2-step testing protocol and can be identified with MS-QMA as a first line test. (C) 2015 American Association for Clinical Chemistry

## Palabras clave

**KeyWords Plus:**POLYMERASE-CHAIN-REACTION; FULL-MUTATION; FMR-1 GENE; MENTAL-RETARDATION; DIRECT DIAGNOSIS; PRE-MUTATION; PREMUTATION; MOSAICISM;PREVALENCE; EXPRESSION

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