Methylation analysis of fragile X-related epigenetic elements may provide a suitable newborn screening test for fragile X syndrome

To the Editor:

In a recent issue of this *Journal*, Coffee et al.¹ provides an overview of tests currently available for detection of the fragile X mutation and their uses. The article emphasizes that CGG-based tests are inappropriate for population-based fragile X newborn screening, because of the counseling and ethical challenges created by the detection of premutation carriers and the detection of females with full mutations who may never develop symptoms. Coffee et al. suggests that testing for aberrant methylation is a preferable option for newborn screening because it avoids the detection of small allele carriers, a significant fraction of whom will be destined to develop late onset conditions, but that quantification of the FMR1 protein might provide the only solution.

We have recently developed a novel PCR-based test that examines methylation patterns of fragile X-related epigenetic elements (FREE) using assisted laser desorption/ionization—time of flight mass spectrometry. The FREE methylation test has been closely related to FMR1 protein expression and identified fragile X syndrome (FXS)-affected males and females with 100% specificity in our small study (75 male and 50 female subjects) consisting of samples from all categories of expanded alleles.² Importantly, the assisted laser desorption/ionization—time of flight-based test has been shown to exclude from detection the subset full mutation females who are clinically unaffected, high functioning males with unmethylated full mutations, and all individuals with gray zone and/or premutation alleles.

Given that there is increasing evidence for the benefits of early diagnosis and treatment for FXS,³ the FREE methylation test may offer an attractive solution to the technical and ethical problems that have prevented the introduction of FXS newborn screening.

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