Is it time to retire fragile X testing as a first-tier test for developmental delay, intellectual disability, and autism spectrum disorder?

To the Editor: We read with great interest the article by Weinstein et al.,[1] "Do the Data Really Support Ordering Fragile X Testing as a First-Tier Test Without Clinical Features?," describing the diagnostic yield of chromosomal microarray (CMA) and fragile X (FX) testing for males with intellectual disability (ID) and/or autism spectrum disorder (ASD) in one health-care system. As stated by the authors, developmental delay (DD), ID, and ASD are a group of highly prevalent neurodevelopmental disorders with strong genetic contributions that account for a large proportion of genomic testing requests. Fragile X syndrome has been reported as the most common source of inherited ID and is caused by a repeat expansion in the X-linked *FMR1* gene. Testing for FX is gene-targeted to establish a diagnosis.[2] Currently, according to the American College of Medical Genetics and Genomics and the American Academy of Pediatrics, the first-tier genetic tests for individuals with DD, ID, and/or ASD include CMA and then FX in males.[2–6] However, with the rapid advancement of clinical genomic testing and the plethora of diagnostic yield studies in the literature, these practice guidelines may need to be revisited. In the study by Weinstein et al.[1] the diagnostic yield for FX testing in males with ID and ASD was 2.5% (2/80) and 0% (0/75), respectively. The limited yield of testing in their cohort supports an ongoing conversation among medical geneticists: should FX testing be considered as a first-tier diagnostic test for individuals with DD, ID, and/or ASD in the absence of syndrome-specific physical findings or a family history suggestive of fragile X etiology?

Our clinical experience at the UCLA Medical Center over the past 15 years has suggested that the yield of FX testing is limited in populations with DD, ID, and ASD.[7] We therefore sought to examine the above observation made by Weinstein et al.[1] through expansion of the total number of cases examined. We performed our own retrospective analysis of males with DD, ID, and/or ASD who underwent diagnostic FX testing from January 2002 to March 2017 at the UCLA Molecular Diagnostics Laboratories. The cohort was identified through a pathology-based electronic medical record system. We excluded all males who were being tested for ataxia with no ID, DD, or ASD. Overall, we identified 654 males ranging in age from 1 to 21 years with DD, ID, and/or ASD who had FX testing. The yield of FX testing for these patients was 0/654 (0%). Our diagnostic yield is comparatively similar to other studies[1,8,9] and is supported by the largest cohort examined to date. The zero diagnostic yield for FX testing in our DD, ID, and/or ASD cohort could be due to cases of FX being excluded from our cohort by early diagnosis from classical symptoms or family history, which supports the concept that FX testing may be warranted particularly in those instances.

Given the rapidly evolving genomic diagnostic testing landscape, it appears imperative that practice guidelines adapt swiftly and accordingly. For example, prior to 2010, guidelines for clinical genetic testing recommended G-banded karyotype as the gold standard test for the detection of chromosomal imbalance in patients with ID, DD, and ASD in addition to FX testing. This was in spite of the frequent use and widespread adoption of chromosomal microarray analysis in clinical practice. It was not until 2010, after a series of large-data-set articles were published on the diagnostic yield of ID, DD, and/or ASD by CMA (determined to be 7–20%[6,8]), that the guidelines were updated to implement CMA as a first-tier diagnostic test.[8] The review of data from our cohort supports the need to revisit the guidelines of genetic evaluation for patients with DD, ID, and ASD, particularly in the era of genome-wide testing.

In conclusion, FX testing should be retired as a first-tier test but remain as part of the differential, particularly when well-defined features (physical and behavioral characteristics) and/or family history suggestive of fragile X syndrome are present. Further, with the advent of next-generation sequencing into clinical laboratories, numerous studies from academic and commercial laboratories have begun to establish the diagnostic utility of exome sequencing, with yields ranging from 10 to 41%[10–13] in ID, DD, and ASD cohorts. Based on the higher diagnostic yields of CMA and exome sequencing in these cohorts, as well as the results of Weinstein et al.[1] and others, we propose that these genome-wide tests become the recommended first-tier tests.

DISCLOSURE

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