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THE PREVALENCE OF FRAGILE X SYNDROME IN INDIVIDUALS WITH AUTISM SPECTRUM DISORDER: GENETIC INSIGHTS AND DIAGNOSTIC CHALLENGES

OTİZM SPEKTRUM BOZUKLUĞU OLAN BİREYLERDE FRAGİLE X SENDROMU PREVALANSI: GENETİK BULGULAR VE TANISAL ZORLUKLAR

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Abstract

Objective: Fragile X Syndrome (FXS) is a complex neurodevelopmental condition characterised by delayed speech development, dysmorphic features, and impaired cognitive development. FXS, which results from CGG repeat expansion in the *FMR1* gene, is one of the most commonly identified genetic cause of autism. Accurate diagnosis of FXS is crucial for effective management and treatment. This study aimed to evaluate the prevalence of FXS in individuals with Autism Spectrum Disorder (ASD).

Material and Methods: We conducted a retrospective study involving 50 patients. Comprehensive fragment analysis of the *FMR1* gene was performed, with repeat sequences classified according to the stringent guidelines established by American College of Medical Genetics and Genomics (ACMG), Clinical Molecular Genetics Society (CMGS) ve European Society of Human Genetics (ESHG).

Results: FXS was identified in three individuals (6%) within the study cohort. This finding aligns with previous reports indicating prevalence rates between 2% and 8% among ASD populations, thereby confirming the significance of our results.

Conclusion: The overlapping symptoms of FXS and idiopathic autism present diagnostic challenges, highlighting the importance of identifying FXS to implement targeted therapies. Family history is critical in identifying at-risk individuals, as FXS can lead to varied manifestations in family members, including ataxia and early menopause. Although this study provides valuable insights,

Öz

Amaç: Fragile X sendromu (FXS), gecikmiş konuşma gelişimi, dismorfik özellikler ve bilişsel gelişimin bozulması ile karakterize karmaşık bir nörogelişimsel durumdur. *FMR1* genindeki CGG tekrar genişlemesi sonucu ortaya çıkan FXS, otizmin en sık belirlenen genetik nedenlerinden birisidir. FXS'nin doğru tanısı, etkili yönetim ve tedavi için büyük önem taşımaktadır. Bu çalışma, otizmli bireylerde FXS prevalansını değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu çalışmada 50 hasta üzerinde yapılan fragman analizi ile *FMR1* genindeki CGG tekrar uzunlukları değerlendirildi. Elde edilen sonuçlar, tekrarlayan bölgelerin American College of Medical Genetics and Genomics (ACMG), Clinical Molecular Genetics Society (CMGS) ve European Society of Human Genetics (ESHG) kılavuzlarına uygun olarak sınıflandırılmasıyla yorumlandı.

Bulgular: Çalışma kohortunda üç bireyde (%6) FXS tespit edilmiştir. Bu bulgu, otizm spektrum bozukluğu popülasyonlarında %2 ile %8 arasında değişen prevalans oranlarını bildiren önceki çalışmalarla uyumlu olup, elde edilen sonuçların önemini doğrulamaktadır.

Sonuç: FXS ile idiopatik otizmin örtüşen semptomları tanısal zorluklar yaratmakta olup, hedefe yönelik tedavilerin uygulanabilmesi için FXS'nin belirlenmesi büyük önem taşımaktadır. Aile öyküsü, risk altındaki bireylerin tanımlanmasında kritik bir rol oynamaktadır. FXS, aile bireylerinde ataksi ve erken menopoz gibi farklı klinik belirtilere yol açabilmektedir. Bu çalışma değerli

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the limited sample size underscores the need for larger-scale research. Advanced genetic investigations and comprehensive panels could further aid in identifying additional causes of autism.

bilgiler sağlasa da, sınırlı örneklem büyüklüğü daha geniş ölçekli araştırmalara olan ihtiyacı vurgulamaktadır. İleri genetik araştırmalar ve kapsamlı paneller, otizmin ek nedenlerinin belirlenmesine daha fazla yardımcı olabilir.

Keywords Fragile X Syndrome · autism spectrum disorder · FMR1 gene · fragment analysis

Anahtar Kelimeler Fragile X sendromu · otizm spektrum bozukluğu · FMR1 geni · fragman analizi

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder that affects an individual's ability to interact, communicate, and engage in repetitive behaviors, also known as stereotypic behaviors. The causes of ASD are diverse and can include both genetic and environmental factors that contribute to its onset and manifestation. One of the most common genetic factors associated with ASD is Fragile X syndrome (FXS), which is the most frequently observed inherited cause of intellectual disability in males, with a prevalence of approximately 1 in 4,000 to 6000 males. FXS occurs due to a mutation in the *FMR1* gene located on the X chromosome, characterised by an expansion of the CGG repeat tract in the 5′-UTR. Full mutations over 200 CGG repeats result in the hypermethylation of DNA, and this mutation leads to a deficiency of fragile X mental retardation protein (FMRP), which is essential for proper brain development and normal synaptic function (1, 2).

In individuals with FXS, a significant proportion exhibit behaviors that overlap with those seen in ASD, including social impairments, stereotypical movements, and repetitive behaviors. Epidemiological studies have revealed that FXS is present in 2%–8% of individuals diagnosed with ASD when genetic testing methods such as DNA analysis are used. On the other hand, the prevalence of ASD in individuals with FXS is notably high, with estimates suggesting that between 15% and 60% of males with FXS meet the diagnostic criteria for ASD, depending on the diagnostic tools used (3, 4).

One of the major challenges in diagnosing ASD in individuals with FXS is the significant overlap between the behavioral characteristics of both conditions. For example, hand flapping, sensory sensitivities, delayed or limited speech ability, and difficulties with social interaction are frequently observed in both FXS and ASD populations. This overlap makes clinical diagnosis difficult and may lead to incorrect or incomplete diagnosis if the underlying genetic condition is not considered. It is important to note that while men with FXS generally exhibit more severe symptoms due to the X-linked inheritance pattern, women with FXS can also exhibit autism-related behaviors, albeit to a lesser degree. Studies have found that up to 60% of men with FXS meet the criteria for ASD, while the incidence in women is significantly lower, ranging from 14% to 17% (3, 5, 6).

Recent studies have employed more refined diagnostic measures, such as the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R), to improve the accuracy of ASD diagnosis in individuals with FXS. These studies have revealed variability in the relationship between the molecular features of FXS, such as the CGG repeat number and FMRP levels, and the severity of ASD-related behaviors (1). Interestingly, while some studies suggest that lower levels of FMRP may correlate with more pronounced autism traits, others report no clear association, suggesting that multiple genetic and environmental factors may influence ASD in FXS (5, 6).

This complex interaction between FXS and ASD highlights the importance of genetic testing in individuals with ASD. Identifying FXS as an underlying cause provides a more accurate diagnosis and informs clinical management, allowing targeted treatments and interventions. Additionally, understanding the prevalence and nature of ASD in individuals with FXS may help provide better-tailored support to these individuals, especially as ASD symptoms may differ in individuals with FXS compared with those with idiopathic autism. In addition, since individuals diagnosed with FXS may be accompanied by connective tissue abnormalities and genitourinary findings such as macroorchidism, follow-up of individuals diagnosed with FXS can be performed more effectively (4, 6, 7).

In light of these findings, this study aims to review the current literature on the prevalence of FXS in individuals with autism, explore the relationship between molecular factors and ASD symptoms, and discuss the clinical implications of these findings for genetic testing and diagnosis.

MATERIALS AND METHODS

Study population

This retrospective study included 50 individuals who were referred to the Medical Genetics Department of Ümraniye Research and Training Hospital between January 2020 and December 2022 for the etiologic evaluation of autism. The institutional review board has approved the study's design and procedures according to the principles outlined in the

Declaration of Helsinki and ethical standards for human experimentation (Date: 12.12.2024, No: 441). Patients were diagnosed with ASD based on the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) criteria, confirmed by a multidisciplinary team including a child psychiatrist and a neurologist. There were no age restrictions for inclusion in the study; individuals of all ages referred for aetiological evaluation of autism were considered. Patients were included if they had no known chromosomal abnormalities, metabolic disorders, or syndromic diagnosis at the time of referral. Those with incomplete clinical data or previously confirmed genetic diagnoses were excluded.

DNA Extraction and fragment analysis

The genomic DNA was purified from peripheral blood using a QIAamp DNA Mini QIAcube Kit (QIAGEN GmbH Germany). The LabGscanTM FRAXA PCR Kit (QIAGEN GmbH, Germany) is based on the triplet repeat primed PCR (TP-PCR), followed by capillary electrophoresis using a Genetic Analyzer for fragment sizing. The analysis was conducted using the ABI 3130 genetic analyzer (Thermo Fisher Scientific, USA), and the data were analysed with GeneMapper Software v4.0 (Applied Biosystems). The test was performed using the FragilEase kit (Perkin Elmer Inc), and the *FMR1* gene was evaluated according to its reference sequence NM_002024.4 (6).

Interpretation and classification

The repeat sequences of the *FMR1* gene were categorised based on the American College of Medical Genetics (ACMG) and Clinical Molecular Genetics Society/European Society of Human Genetics (CMGS/ESHG) guidelines in Table 1 (7, 8). The repeat sequences were evaluated, considering the patient's clinical indication and gender. The size of the target amplicon was determined by comparing it with a co-injected size standard. The LabGscan™ FRAXA PCR kit (Labgenomics, Korea) included two correction factors for size conversion. To account for the differential mobility, the base pair sizes for each allele were adjusted based on the number of CGG repeats. The product peak sizes were then converted to repeat lengths using the following equation:

*CGG Repeats = *(Peak-c)/m* (*Peak – size in base pairs of a given product peak, *c – size correction factor, *m – mobility correction factor for each CGG repeat)

Confirmation and limitations

It is important to note that this test has certain limitations, including sensitivity and specificity constraints. Due to these limitations, false negative/positive results are possible. Moreover, other genetic factors that may contribute to the disease outside the test panel should be considered. Other genes or genomic regions not yet associated with the disease could also be responsible for the clinical presentation, which is not detectable by the current test.

Table 1. Allele classification according to the American College of Medical Genetics and the European Molecular Genetics Quality Network.

Allele classification	CGG repeat expansion
Normal	<45/<50
Intermediate (Gray zone)	45–54/50–58
Premutation (Meiotic instability)	55–200/59–200
Full mutation	>200/>200

RESULTS

A total of 50 patients, four girls and 46 boys, participated in the study with a preliminary diagnosis of autism. The average age was eight years, the youngest patient was two years old, and the oldest patient was 27 years old. Besides autism, the most common accompanying clinical conditions were epilepsy and behavioral disorders. There was accompanying epilepsy in seven cases. The accompanying symptom in the second stage was a delay in language development. In this study, 50 patients were analysed for FXS using fragment analysis. Among these, FXS was identified in three individuals, representing 6% of the study population.

FXS was not detected in any of the four female cases. Three patients were diagnosed with FXS, and all of these patients were male. Additionally, one male patient was detected as a premutation carrier.

Case 1

He was born as the second child of consanguineous parents and was diagnosed with autism at the age of two. The patient exhibited dysmorphic features commonly associated with FXS, including a coarse face, large forehead, long face, prominent jaw, and large ears. At the age of 17, he was diagnosed with FXS, and testing revealed that the CGG repeats on the *FMR1* allele were 273 (Figure 1). His mother is a premutation carrier with 30,85 CGG repeats. She experienced early menopause at the age of 32 years and has multiple Café-au-lait macules on her body.

Case 2

He was born as the first child of nonconsanguineous parents. He was diagnosed with autism and intellectual disability. He had an umbilical hernia, joint laxity, and dysmorphic features such as large, anteverted ears. He was diagnosed with FXS at the age of three years, and CGG repeats on the *FMR1* allele were determined as 277 (Figure 2) (approximately +- values will be given), and his mother also had 29,276 CGG repeats.

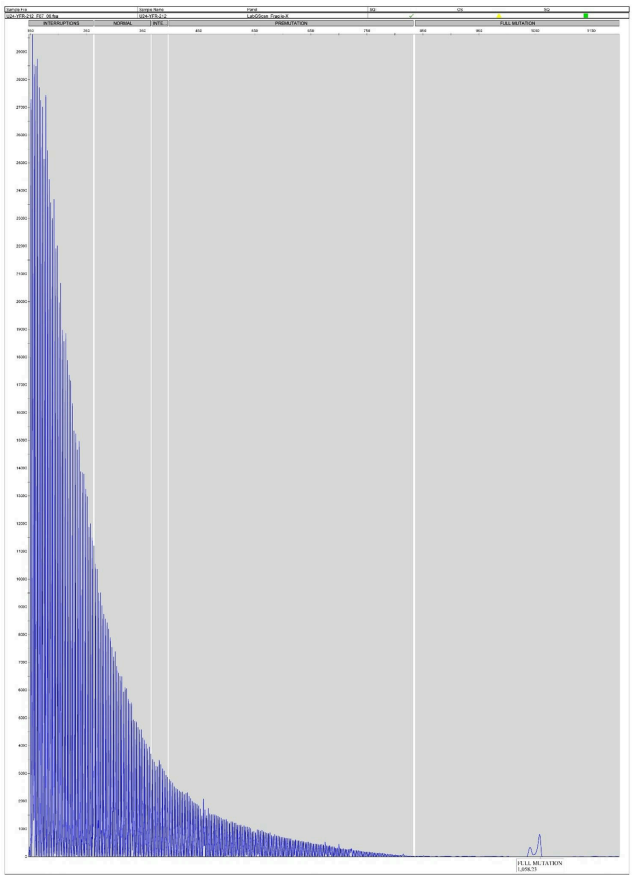

Figure 1. Fragment analysis results of the *FMR1* gene. Case 1 presented with a full mutation.

Case 3

He was born at term and his parents were not consanguineous. He was born with kidney stones, and there is a family history of kidney stones on his maternal uncle's side. He was five years old when he presented to the clinic due to mental retardation and epilepsy, and he had not yet started speaking. His dysmorphic features include a long face, anteverted ears, and epicanthal folds. He was diagnosed with FXS at age five, and CGG repeats on the *FMR1* allele were determined as 228 (Figure 3).

Case 4

He was a premutation carrier with 87 CGG repeats on the *FMR1* allele (Figure 4). He was two years old when he was referred to the medical genetics clinic because of a family history of FXS diagnosed in his brother. He had a mild developmental delay, and his language development was also delayed compared to his chronological age.

DISCUSSION

This study investigated the prevalence of FXS in individuals diagnosed with ASD through genetic analysis of the *FMR1* gene. Among 50 patients analyzed, FXS was identified in three individuals, representing 6% of the study population. This finding is consistent with the existing literature, which estimates the prevalence of FXS in individuals with ASD to range between 2% and 8% when using DNA-based testing (1, 6, 9).

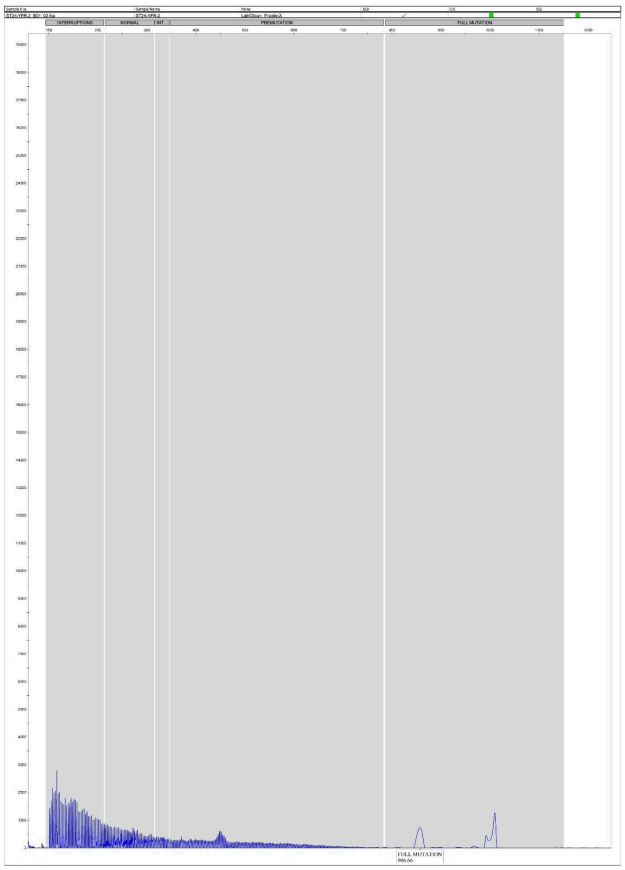

Figure 2. Fragment analysis results of the *FMR1* gene. Case 2 presented with a full mutation.

The phenotypic characteristics observed in patients with FXS in this study align with those reported in previous research. Dysmorphic features such as anteverted ears, a long face, and epicanthal folds, along with neurodevelopmental delays and epilepsy, are well-documented markers of FXS. Delayed language development, a common feature of FXS, was also evident in this cohort. The overlap of symptoms with ASD presents diagnostic challenges, emphasising the need for heightened awareness of FXS in individuals presenting with developmental delays (1, 10).

Although some studies have reported a correlation between FMRP levels and autistic traits (Hatton et al., 2006), this relationship remains a topic of debate. For instance, Rogers et al. and Bailey et al. suggest that autistic behaviors observed in individuals with FXS may not be solely attributed to *FMR1* mutations but may also involve additional genetic or environmental factors (11, 12). Furthermore, findings by Hessl

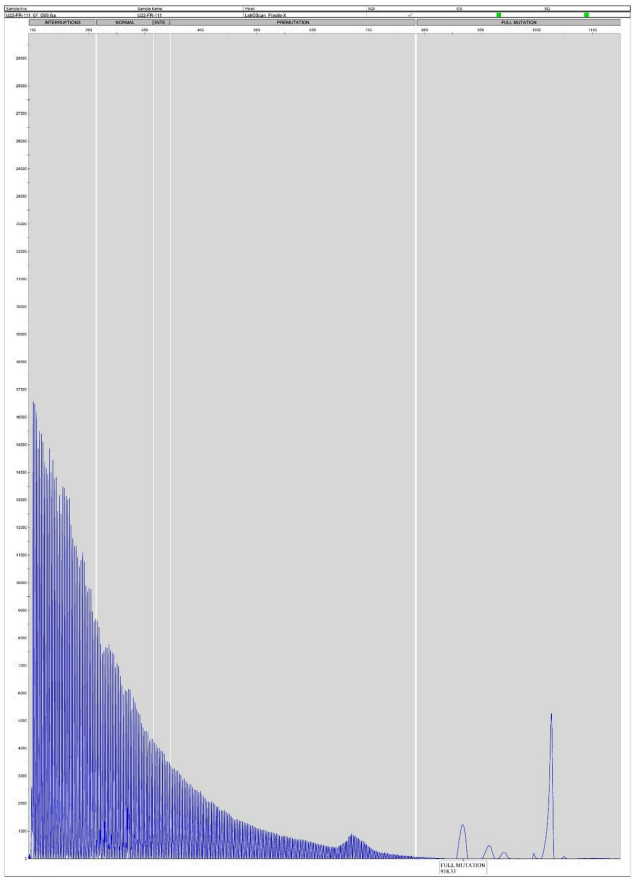

Figure 3. Fragment analysis results of the *FMR1* gene. Case 3 presented with a full mutation.

et al. indicate that the association between FMRP levels and autism symptoms may diminish or disappear when controlling for intellectual functioning (13). These inconsistent results across studies suggest that there is currently no clear consensus in the literature regarding the direct influence of FMRP levels on the severity of autism-related behaviors in individuals with FXS. In our study, the limited sample size prevented us from contributing definitive evidence to this ongoing debate (11-13).

Given the complex and multifactorial nature of FXS-related phenotypes, including autism symptoms, it is essential to also consider the underlying genetic mechanisms, such as CGG repeat expansions and their transmission dynamics across generations. Mothers who are carriers of the *FMR1* premutation typically have CGG repeat expansions ranging from 55 to 200 repeats. The premutation can expand further during meiosis, particularly in oocytes, increasing the CGG repeat count beyond 200, resulting in a full mutation. This expansion silences the *FMR1* gene through methylation, leading to reduced or absent production of the FMRP. The lack of FMRP disrupts normal neural development, significantly affecting the child's cognitive and behavioral functions (9, 14). The higher the CGG repeat count within the premutation range, the greater the risk of expansion to a full mutation. For instance, a mother with 90 CGG repeats has a higher likelihood of passing on a full mutation compared with a mother with 60 CGG repeats (7, 10). In the first case, although the mother was a premutation carrier with 85 CGG repeats, we observed a significant expansion of the repeat count in her son, reaching 273 repeats.

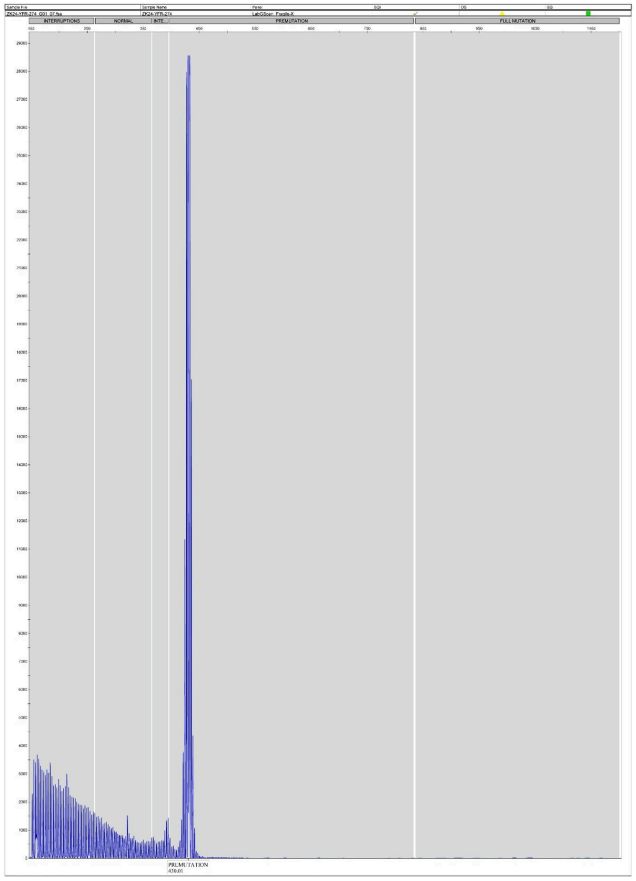

Figure 4. Fragment analysis results of the *FMR1* gene. Case 4 presented with a premutation.

A significant finding from this study is the impact of family history in identifying individuals at risk. Cases that were referred because of a family history of FXS or related conditions were more likely to produce positive results. This underscores the importance of thorough clinical and family assessments in guiding genetic evaluations. It also emphasises the value of targeted genetic counseling to optimise diagnostic pathways and effectively allocate resources.

Additionally, while this study focused on the *FMR1* gene, ASD is a highly heterogeneous condition with numerous genetic contributors. Recent studies have highlighted the diagnostic value of various genetic tests in the evaluation of ASD. Chromosomal microarray analysis (CMA), recommended as a first-tier test by several professional guidelines, demonstrates

a diagnostic yield of 10%–20%, identifying pathogenic copy number variants associated with neurodevelopmental disorders. Whole exome sequencing (WES), although more expensive and less accessible, offers the highest diagnostic yield, ranging from 15%–30%, by detecting single-nucleotide variants and small indels in known ASD-associated genes (Table 2). Despite its relatively lower yield and resolution, *FMR1* testing remains cost-effective and clinically relevant, especially when used early in a stepwise diagnostic algorithm or settings with limited access to comprehensive genomic technologies. This underscores the continued importance of fragment analysis in the genetic evaluation of ASD, alongside more advanced technologies (6, 14).

Table 2. Diagnostic yields of common genetic tests used in ASD.

Test	Diagnostic yield (%)
FMR1 fragment analysis	1–6
Array-CGH	10–20
WES	15–30
WGS	25–40+

FMR1: Fragile X Messenger Ribonucleoprotein 1 Gene, Array-CGH: Microarray-based comparative genomic hybridisation, WES: Whole exome sequencing, WGS: Whole genome sequencing

CONCLUSION

In conclusion, this study emphasises the significance of genetic testing for FXS in individuals with ASD, particularly those with a positive family history or neurodevelopmental delays. Although comprehensive techniques such as WES and WGS are increasingly used as first-tier tests, our findings emphasise that traditional methods like fragment analysis for FXS should not be overlooked. Prioritising this approach as an initial diagnostic step can help prevent missed diagnoses, reduce costs, and streamline the evaluation process, reinforcing the clinical value of a stepwise, algorithmic diagnostic strategy even in today's era of advanced genomic technologies (1, 7, 14).

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Umraniye Research and Training Hospital (Date: 12.12.2024, No: 441).

Informed Consent: Consent was obtained from all participants who participated in the study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- İ.K., Ç.D., L.A.C., A.B., N.B.A.; Data Acquisition- İ.K., Ç.D., L.A.C., A.B., N.B.A.; Data Analysis/Interpretation – İ.K., Ç.D.; Drafting Manuscript- İ.K.; Critical Revision of Manuscript- İ.K., Ç.D.; Final Approval and Accountability- İ.K., Ç.D., L.A.C., A.B., N.B.A.

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