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Dystonia Genetics in the Southeastern Anatolia Region of Türkiye

Türkiye'nin Güneydoğu Anadolu Bölgesindeki Distoni Genetiği

Mehmet Burak Mutlu[1], Özlem Öz[2]

[1]Detagen Genetic Diseases Evaluation Center, Kayseri, TÜRKİYE
[2]Harran University Medical Faculty, Medical Genetics Department, Şanlıurfa, TÜRKİYE

Abstract

Background: Dystonia is a term used to describe hyperkinetic movement disorders in which dystonia is the prominent feature. Depending on the aetiology, dystonia may be acquired, inherited, or idiopathic. The dystonia genes that are usually involved in these pathways are classified as isolated, complex, and combined dystonia genes. In this study, we investigate the genetic causes of dystonia in 60 patients by whole-exsome sequencing (WES). Genotype-phenotype correlation of the obtained results was performed.

Materials and Methods: Sixty patients (25 females, 35 males) were included in the study who were referred to Harran University Medical Faculty Hospital between 2021 and 2025. Patients were selected based on the presence of symptoms of dystonia. We performed WES and evaluated the variants with recommended guidelines.

Results: WES analysis revealed the presence of pathogenic or likely pathogenic mutations in 17 patients (approximately 28%) of the cohort. 37 patients (approximately 62%) exhibited variants of uncertain clinical significance (VUS). In 6 patients (10%), WES did not reveal any variations associated with dystonia.

Conclusions: This study emphasises the pivotal function of genetic testing in the diagnosis and management of dystonia in the southern-eastern Anatolian region. The identification of specific genetic variants facilitates the implementation of personalised treatment strategies, which has the potential to enhance therapeutic outcomes and reduce adverse effects.

Keywords: Dystonia, Whole-exome sequencing, WES, NGS

Öz

Amaç: Distoni, distoninin belirgin bir özellik olduğu hiperkinetik hareket bozukluklarını tanımlamak için kullanılan bir terimdir. Etiyolojiye bağlı olarak distoni, edinilmiş, kalıtsal veya idiyopatik olabilir. Bu yollarda genellikle rol oynayan distoni genleri, izole, kompleks ve kombine distoni genleri olarak sınıflandırılır. Bu çalışmada, 60 hastada distoninin genetik nedenlerini tüm eksom dizileme (WES) ile araştırdık. Elde edilen sonuçların genotip-fenotip korelasyonu yapıldı.

Materyal ve Metod: Çalışmaya, 2021 ile 2025 yılları arasında Harran Üniversitesi Tıp Fakültesi Hastanesi'ne sevk edilen 60 hasta (25 kadın, 35 erkek) dahil edildi. Hastalar distoni semptomlarının varlığına göre seçildi. WES uyguladık ve önerilen kılavuzlara göre varyantları değerlendirdik.

Bulgular: WES analizi, kohortun 17 hastasında (yaklaşık %28) patojenik veya muhtemelen patojenik mutasyonların varlığını ortaya çıkardı. Otuz yedi hasta (yaklaşık %62) klinik önemi belirsiz varyantlar (VUS) sergiledi. 6 hastada (%10) WES, distoni ile ilişkili herhangi bir varyasyon saptamadı.

Sonuç: Bu çalışma, Güneydoğu Anadolu Bölgesi'nde distoninin tanı ve tedavisinde genetik testlerin önemli rolünü vurgulamaktadır. Spesifik genetik varyantların tanımlanması, kişiselleştirilmiş tedavi stratejilerinin uygulanmasını kolaylaştırır ve bu da tedavi sonuçlarını iyileştirme ve yan etkileri azaltma potansiyeline sahiptir.

Anahtar Kelimeler: Distoni, Tüm ekzom dizileme, WES, NGS

Corresponding Author: Mehmet Burak Mutlu, Detagen Genetic Diseases Evaluation Center, Kayseri, TÜRKİYE
E-mail: dr.mutluburak@gmail.com / **ORCID ID:** 0000-0001-7745-8165
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Introduction

Dystonia is a term used to describe hyperkinetic movement disorders in which dystonia is the prominent feature. Depending on the aetiology, dystonia may be acquired, inherited, or idiopathic. It is recommended that the findings examination concentrate on the five classic physical signs of dystonia syndromes. These signs can be categorised as follows: two main physical signs (dystonic movements and dystonic posture); and three additional physical signs (mirror dystonia, overflow dystonia, and geste antagonists/sensory tricks) (1). According to recent epidemiological studies, the prevalence of isolated dystonia was estimated at 52.7/100,000 or 30.9/100,000 (2,3). However, it is important to note that the true prevalence of this condition may be significantly higher than reported, as many cases may remain undiagnosed or misdiagnosed. It is noteworthy that the majority of subforms exhibit a higher prevalence among females (2). The dystonia mechanisms are diverse and mainly affect gene transcription during neurodevelopment, the ER stress response-autophagy, striatal dopamine signalling, and calcium homeostasis (4). The dystonia genes that are usually involved in these pathways are classified as isolated, complex, and combined dystonia genes (5,6). In this study, we investigate the genetic causes of dystonia in 60 patients by whole exome sequencing (WES). Genotype-phenotype correlation of the obtained results was performed.

Materials and Methods

This study, approved by the Ethics Committee of the Faculty of Medicine, Harran University *(approval no: HRÜ/25.09.55, date: May 12, 2025):* included 60 patients (25 females, 35 males) who were referred to Harran University Medical Faculty Hospital between 2021 and 2025. Patients were selected based on the presence of symptoms of dystonia. WES test was applied to patients. The patient's genome underwent enrichment using the Twist Library Preparation Kit from fragmented genomic DNA. Subsequently, the library generated was subjected to sequencing on the Illumina platform, achieving an average coverage depth ranging from 70x to 100x. The raw data produced through Next Generation Sequencing (NGS) was processed using bioinformatics tools in alignment with the reference genome GRCh37 (hg19). The assessment focused on the protein-coding exonic sequence and the ±10 bp intronic region proximal to the exons. The analyses primarily utilized in silico tools such as Revel, AlphaMissense, Eve, MUT Assesor, SIFT, MutationTaster, FATHMM, DANN, MetaLR, PrimateAI, BayesDel, SpliceAI, GERP, GenoCanyon, and fitCons. The guideline established by the American College of Medical Genetics and Genomics (ACMG) was used to describe the variants' pathogenicity (7).

Results

Our study included 60 dystonia patients; 25 were females (approximately 42%) and 35 were males (approximately 58%). A detailed analysis revealed the presence of pathogenic or likely pathogenic mutations in 17 patients (approximately 28%). Notwithstanding the fact that 37 patients (approximately 62%) exhibited variants of uncertain clinical significance (VUS), these were not incorporated in the assessment of the genetic aetiology rate. In 6 patients (10%), WES did not reveal any variations associated with dystonia. The pathogenic and likely pathogenic variants detected in the patients are shown in Table 1.

Table 1. The pathogenic and likely pathogenic variants

Patient	Gene	Transcript	cDNA	Zygosity	Classification
Patient 1	ADPRS	NM_017825.3	c.2353A>C	Homozygous	Likely Pathogenic
Patient 2	ARID1B	NM_001374828.1	c.5689_5702delinsA	Heterozygous	Likely Pathogenic
Patient 3	ARID2	NM_152641.4	c.265_266del	Heterozygous	Likely Pathogenic
Patient 4	ATP1A3	NM_152296.5	c.2266C>T	Heterozygous	Pathogenic
Patient 5	GNAL	NM_182978.4	c.150del	Heterozygous	Likely Pathogenic
Patient 6	SGCE	NM_003919.3	c.289C>T	Heterozygous	Pathogenic
Patient 7	SGCE	NM_003919.3	c.272T>G	Heterozygous	Pathogenic
Patient 8	SLC2A1	NM_006516.4	c.1370G>T	Heterozygous	Likely Pathogenic
Patient 9	SLC2A1	NM_006516.4	c.516+1G>A	Heterozygous	Likely Pathogenic
Patient 10	SLC2A1	NM_006516.4	c.376C>T	Heterozygous	Pathogenic
Patient 11	SPR	NM_003124.5	c.354_355delTCinsCT	Heterozygous	Likely Pathogenic
Patient 12	SPR	NM_003124.5	c.596-2_602del	Homozygous	Likely Pathogenic
Patient 13	SPR	NM_003124.5	c.517G>A	Homozygous	Likely Pathogenic
Patient 14	SPR	NM_003124.5	c.448_452del	Heterozygous	Pathogenic
Patient 15	TOR1A	NM_000113.3	c.845del	Heterozygous	Likely Pathogenic

Segregation analyses were performed on patients Patient 2 and Patient 13 using the Sanger method. The parents of Patient 2 were found to be wild-type normal, while the parents of Patient 13 were found to be heterozygous carriers. Upon analysis of the distribution of patients who have pathogenic or likely pathogenic variants according to the type of dystonia, it was found that 2 patients had myoclonic dystonia, 8 patients had isolated dystonia types, 3 patients had a syndrome, and 4 had sepiapterin reductase deficiency. As illustrated in Table 2, the diagnoses of patients with pathogenic or likely pathogenic variants are outlined below.

Table 2. The diagnosis of patients with pathogenic or likely pathogenic variants

Patient	Disease	OMIM
Patient 1	Neurodegeneration with Variable Ataxia and Seizure, Childhood-onset, Stress-induced	OMIM # 618170
Patient 2	Coffin-Siris Syndrome 1	OMIM # 135900
Patient 3	Coffin-Siris Syndrome 6	OMIM # 617808
Patient 4	Dystonia 12	OMIM # 128235
Patient 5	Dystonia 25	OMIM # 615073
Patient 6	Dystonia 11, Myoclonic	OMIM # 159900
Patient 7	Dystonia 11, Myoclonic	OMIM # 159900
Patient 8	Dystonia 9	OMIM # 601042
Patient 9	Dystonia 9	OMIM # 601042
Patient 10	Dystonia 9	OMIM # 601042
Patient 11	Dystonia, Dopa-Responsive, Due to Sepiapterin Reductase Deficiency	OMIM # 612716
Patient 12	Dystonia, Dopa-Responsive, Due to Sepiapterin Reductase Deficiency	OMIM # 612716
Patient 13	Dystonia, Dopa-Responsive, Due to Sepiapterin Reductase Deficiency	OMIM # 612716
Patient 14	Dystonia, Dopa-Responsive, Due to Sepiapterin Reductase Deficiency	OMIM # 612716
Patient 15	Dystonia 1, Torsion	OMIM # 128100
Patient 16	Dystonia 30	OMIM # 619291
Patient 17	Dystonia 30	OMIM # 619291

Discussion

The present study, which was conducted in southern-eastern Anatolia, provides a detailed analysis of the WES results obtained from 60 dystonia patients. The utilisation of NGS for diagnostic purposes in cases of dystonia has been demonstrated to be both efficacious and beneficial. It is evident that within this field, both panel tests and WES tests are utilised with considerable frequency. The decision to request WES in order to reach a diagnosis should be made when panels for dystonia fail to detect causative mutations. Zech et al. (8) proposed an algorithm that has the potential to predict the success rate of WES in relation to dystonia characteristics. In the event of the summary score attaining a value of the threshold, the utilisation of WES is advised, on account of the elevated probability of identifying causative mutations (8). Whilst third-generation long-read sequencing methods are utilised for the diagnosis of dystonia, they are not employed in routine diagnostic procedures (9).

A wide range of diagnostic rates have been reported in the literature concerning WES studies of patients with dystonia, primarily due to the diversity of the number and types of dystonia of patients studied (8,10). The rate of diagnosis of WES testing for dystonia is estimated to vary between 8% and 37% (8,11–14). We detected pathogenic or likely pathogenic variants in accordance with the literature, approximately 28% in patients. In these mutations, 6 mutations are novel variations and have not been previously documented in the literature, dbSNP, or ClinVar (ARID1B: c.5689_5702delinsA, ARID2: c.265_266del, GNAL: c.150del, SLC2A1: c.1370G>T, SPR: c.517G>A, TOR1A: c.845del).

In the course of classification and reporting a variant, pathogenic variants in the in-house databases of clinical laboratories, the published literature, and de novo variants (parental samples test negative or independent of parental test result) are of value (7). Consequently, it is anticipated that these alterations will prove to be of significant value in the evaluation of variants in subsequent dystonia patients.

Also, the SGCE: c.272T>G and SPR: c.354_355delTCinsCT variants were documented on a single occasion and subsequently confirmed on a second occasion in our present cases (15,16).

Although the TOR1A c.845del variant is novel, there are published cases reporting other pathogenic changes affecting the same amino acid residue(17).

Conclusion

This study emphasises the pivotal function of genetic testing in the diagnosis and management of dystonia in the southern-eastern Anatolian region. The identification of specific genetic variants facilitates the implementation of personalised treatment strategies, which has the potential to enhance therapeutic outcomes and reduce adverse effects. As genetic testing technologies evolve and research in this area expands, there is considerable potential for the development of more precise and personalised treatments for dystonia. The subsequent publishing of the variants detected in the aforementioned studies is of significant importance to the process. The identified novel variants will serve as a guide for the assessment of pathogenicity in future patient cases. VUS present significant diagnostic challenges due to their ambiguous clinical relevance. Nevertheless, as a result of ongoing progress in the field of genetic research and the accumulation of global data, the pathogenic potential of VUS may become more apparent.

Ethic Approval: *This study was approved by the Harran University Clinical Research Ethics Committee (approval no: HRÜ/25.09.55, date: May 12, 2025).*

Author Contributions:

Concept: M.B.M., Ö.Ö.

Literature Review: M.B.M., Ö.Ö.

Design: M.B.M., Ö.Ö.

Data acquisition: M.B.M., Ö.Ö.

Analysis and interpretation: M.B.M., Ö.Ö.

Writing manuscript: M.B.M., Ö.Ö.

Critical revision of manuscript: M.B.M., Ö.Ö.

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