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Case Report

Muscular Dystrophy-Dystroglycanopathy with a Homozygous Pathogenic Variant in the *TMEM5* Gene

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Abstract:

Alpha-dystroglycanopathies encompass a heterogeneous array of neuromuscular diseases arising from aberrant glycosylation of alpha-dystroglycan. These conditions have been linked to many glycosyltransferases, including TMEM5. A hereditary autosomal recessive (AR) condition has been linked to the *TMEM5* gene. Three siblings who have high blood creatine kinase levels and congenital muscular dystrophy were described. Next-generation sequencing (NGS) analysis was used for genetic diagnosis. A noteworthy feature of the clinical trajectory was the somewhat heavier instances with concurrent ocular or cerebral abnormalities. A homozygous mutant area of exon 1 in the *TMEM5* gene, c.139del (p.Ala47Argfs*42) frameshift variant, was discovered by NGS. This variation (nonsense) may impact the synthesis or function of proteins by degrading RNA (PVS1). Public data banks did not contain the variation (PM2). In the ClinVar database, all groups categorized the variation as pathogenic/likely pathogenic without supporting data (PP5). This work highlights the importance of *TMEM5* in disease pathogenesis while broadening the clinical and mutation range of alpha-dystroglycanopathies. Our research sheds light on the molecular causes of dystroglycanopathies linked to *TMEM5*, provides guidance for future treatment approaches, and emphasizes the significance of thorough genetic testing for clinical care.

Key words: muscular dystrophy; dystroglycanopathy; *tmem5* gene; ngs

Introduction

Congenital muscular dystrophies, referred to as dystroglycanopathies, are a group of diseases that vary in both clinical and genetic characteristics. These disorders range in severity from more severe types that frequently include ocular and brain deformities to less severe versions that don't influence the nervous system [1]. Alpha-dystroglycan is a critical cell surface receptor that mediates interactions with extracellular matrix proteins, including laminins. Its improper glycosylation is key to their pathophysiology. Alpha-dystroglycan's regular ligand-binding activity is disrupted by glycosylation dysfunction, which sets off a series of pathogenic processes [2]. Cobblestone lissencephaly, a defining feature of severe types of dystroglycanopathies, is caused by a disruption in the glia limitans, the brain's outermost sub-pial layer [3]. This condition, which represents the most severe forms of congenital muscular dystrophy, is pathognomonic for conditions including Walker-Warburg syndrome (WWS), muscle-eye-brain (MEB) disease, and Fukuyama congenital muscular dystrophy [4]. The majority of children afflicted with WWS pass away before becoming three years old, making it a disease with a dire prognosis [5,6]. Thanks to developments in molecular research, the genetic landscape of WWS has been greatly enlarged, with up to eighteen distinct genes being implicated in its etiology [7,8]. The incidence of genetic diseases, such as WWS, is elevated in consanguineous marriages, underscoring the significance of genetic screening and counseling before matrimony [8]. Neuroimaging is crucial in the diagnostic workup of whole-exome sequencing (WES), even if its use in molecular diagnostics is rising. In addition to facilitating targeted genetic screening and counseling and helping with accurate diagnosis and prognostication, comprehensive analysis and reporting of neuroimaging phenotypes may also lower the occurrence of afflicted children [9]. Durastrophin-glycoprotein complex integrity in the sarcolemma depends on dystrophin-glycan, a transmembrane protein with alpha and beta subunits. A wide range of congenital muscular dystrophies known as alpha-dystroglycanopathies are caused by dysregulation in the glycosylation of alpha-dystroglycan, and TMEM5 has emerged as a key participant in this field [9]. The transmembrane protein TMEM5 is encoded and acts as a xylosyltransferase in the alpha-dystroglycan glycosylation pathway [10]. An autosomal recessive type of congenital muscular dystrophy-dystroglycanopathy, marked by abnormalities of the brain and eyes, has been linked to mutations in *TMEM5* [11]. *TMEM5* mutations have a wide

range of clinical symptoms, from moderate to severe, and some of these instances cause early mortality [12]. We provide a case study of a family afflicted with dystrophy-dystroglycanopathy due to homozygous pathogenic variation in the *TMEM5* gene in this study. Our goals are to characterize the clinical phenomenology of afflicted members of this family and to broaden the mutational range of dystroglycanopathies linked with *TMEM5*.

Peripheral blood samples were collected after obtaining written informed consent. Genomic DNA was extracted from EDTA-anticoagulated peripheral blood by using Standard methods. DNA extraction from blood samples was done using the semi-automated robot as recommended by the manufacturer (Qiagen). The DNA samples' concentration and quality control (260/280 nm and 260/230 nm values) were determined by fluorometrically (Qubit v3.0) and UV spectrophotometry. Amplification of the gene region(s) associated with the disease by chain polymerase reaction (PCR) involves sequencing this region using next-generation sequencing technology. For this purpose, Twist Human Cor e Exome v2 by Sophia Genetics kit is used. The sequencing reaction is carried out using the Illumina NextSeq® system and compatible reagent kits. Raw data were analyzed via the Sophia DDM® data analysis platform. Alignment and variant findings were performed by Pepper®, a proprietary foundation algorithm from Sophia Genetics, based on the hg19 human genome reference. Variant annotation was performed with Sophia Genetics' MOKA® software and for each variant, the effect of the variant on protein sequence (missense, stop gain, etc.), the incidence in various populations (1000G, ESP, ExAC, gnomAD), prediction algorithms (SIFT, PolyPhen) Withthis, information such as the destructive effect of the variant was added. CNV detection was performed with Sophia Genetics' MUSKAT® software. For variant classification, the expert study groups of the Clinvar database (Ensembl VEP; CIMBA; ENIGMA; PharmGKB; CFTR2; ClINGEN-RAS) and the database (CMP-EP) created by Maxwell et al, were taken as references. For other variants not found in the databases, the criteria established by Maxwell et al were considered. The criteria were determined based on the American College of Medical Genetics and Genomics (ACMG) sequencing/sequence variants classification guidelines [13]. For PP2 and BP1 evidence determined at the gene level, the effect of missense variants on the mechanism of the disease was calculated by considering the Pathogenic/Likely pathogenic variants in the Clinvar database. For evidence of PVS1, whether the gene's disease mechanism is predominantly loss of function (LOF) was determined by literature review. Allele frequency thresholds for BA1, and BS1 evidence were determined by a disease-based literature review. The allele frequency threshold value used in PM2 evidence was taken as 0.0001 [14].

Case presentation

Sibling 1: A 30-year-old female patient, the first child of the family, has a neuromotor developmental delay. The patient has vision loss in the left eye, and in her medical history, she was born with a normal spontaneous birth weighing 3500 grams. She could not hold her head in the first 3 months. She started to sit up at about 1 year old and walked when she was around 3. Significant hydrocephalic dilatation was observed in the 3rd and 4th ventricles and frontal horns of her non-contrast cranial CT image (Figure 1). She did not speak or express herself, however, her hearing was normal and she had no seizures.

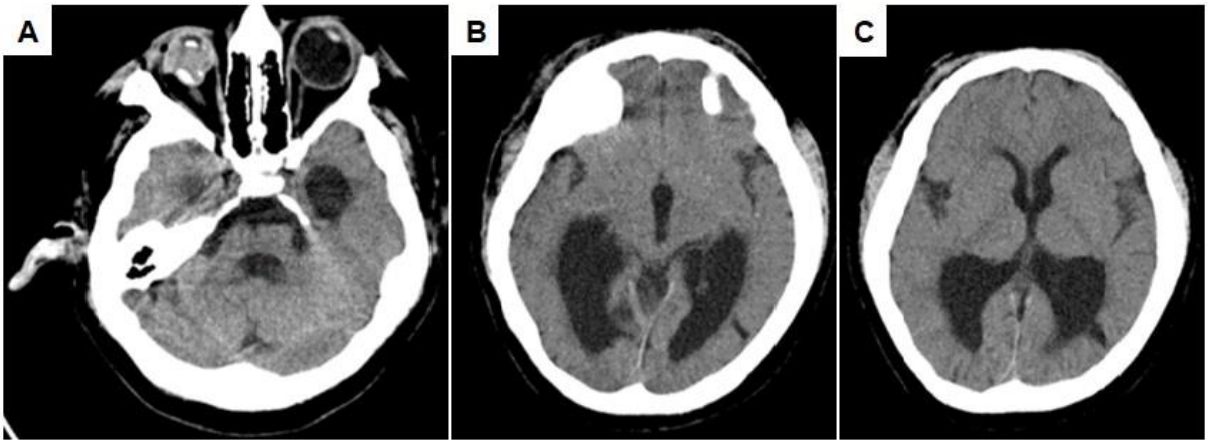

Figure 1: Non-contrast cranial CT in sibling 1: The occipital horns of both lateral ventricles were observed to be wide corpus cephalic (**A–C**). Cystic porencephalic changes with irregular borders extending to the cortex in connection with the occipital horn of the left lateral ventricle were noteworthy. Additionally, significant hydrocephalic dilatation was observed in the 3rd and 4th ventricles and frontal horns. Cisterna magna was widely observed.

Sibling 2: A 27-year-old female patient, the second child of the family. In her medical history, neuromotor development stages were delayed. Her development was normal until the age of 1, but then there was a pause in her development. She walked at the age of 2.5, her speech started after the age of 6, and she is limited to one or two words, and cannot express herself. There was no history of seizures. In her neurological examination, muscle strength was 4/5 in the distal and proximal upper extremities, -4/5 in the lower extremity, deep tendon reflex (DTR) could not be obtained in the lower extremity, and her gait was ataxic. She could not fully express herself, had no speech, and had repetitive movements.

Sibling 3: A 19-year-old male patient, the last child of the family, who has a neuromotor developmental delay like his siblings, and has milder symptoms than his siblings. He started walking after the age of 3 and can express himself, albeit slightly. He has a history of febrile seizures at the age of 1 year, his EEG was found to be within normal limits, and he is being followed up by Pediatric Psychiatry due to his hyperactivity. On neurological examination, muscle strength was 4/5 in the upper extremity, no DTR was obtained, +4/5 in the lower extremity, DTR was hypoactive, slightly ataxic, and there was incompetence in cerebellar tests. Creatine kinase values were found to be high, and there was cerebellar atrophy in the patient's cranial MRI (Figure 2). Vision and hearing examinations were normal.

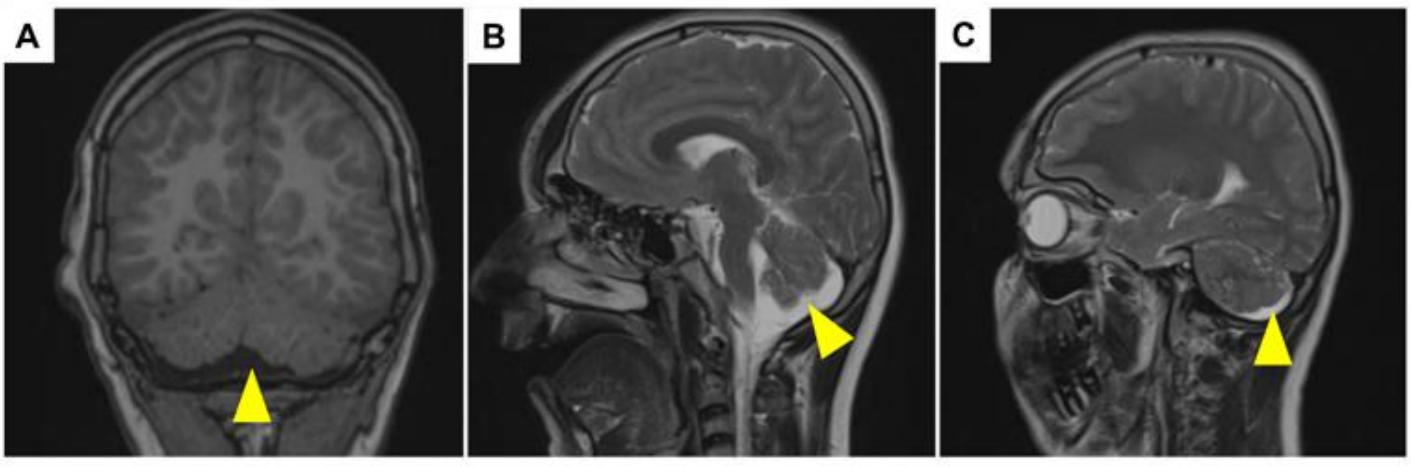

Figure 2: Brain MRI in a patient, Sibling 3, with chronic muscular dystrophy carrying a mutation in *TMEM5*. (**A–C**) Coronal and sagittal images showing cerebellar anomalies with yellow arrowheads.

In all three cases, the following RXYLT1 (*TMEM5*) variant was found to be homozygotic. The c.139del p.(Ala47Argfs*42) frameshift variant was detected as homozygous in the *TMEM5* gene. Variant (nonsense, frameshift, splice site ±1, 2) may cause RNA degradation and affect protein formation or function (PVS1). The variant was not seen in public data banks (ExaC, ESP, 1000G) (PM2). The variant was classified as pathogenic/likely pathogenic by all groups in the ClinVar database without evidence (PP5). The *TMEM5* gene is associated with AR inherited disease *Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 10* in the OMIM database (Figure 3) (Figure 4) (Table 1)

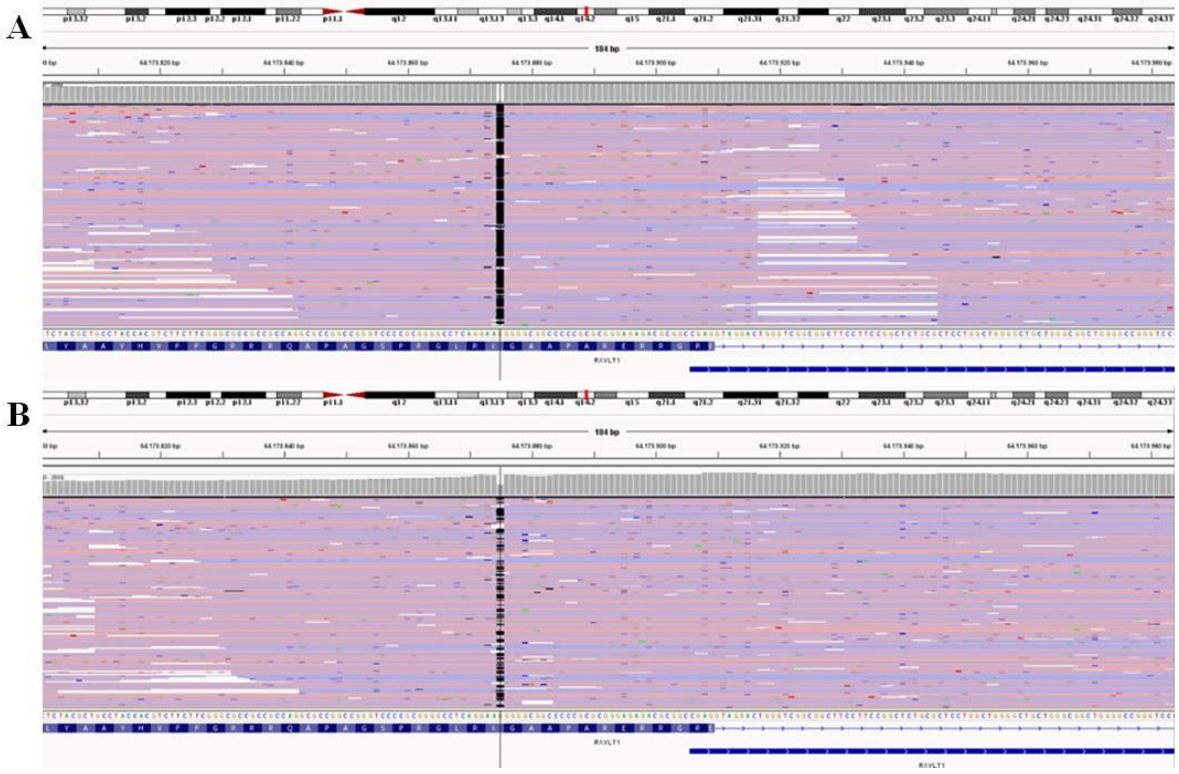

Figure 3: Intergenomic variations of the *TMEM5* mutated family. **A** is for three siblings. **B** is for their parents.

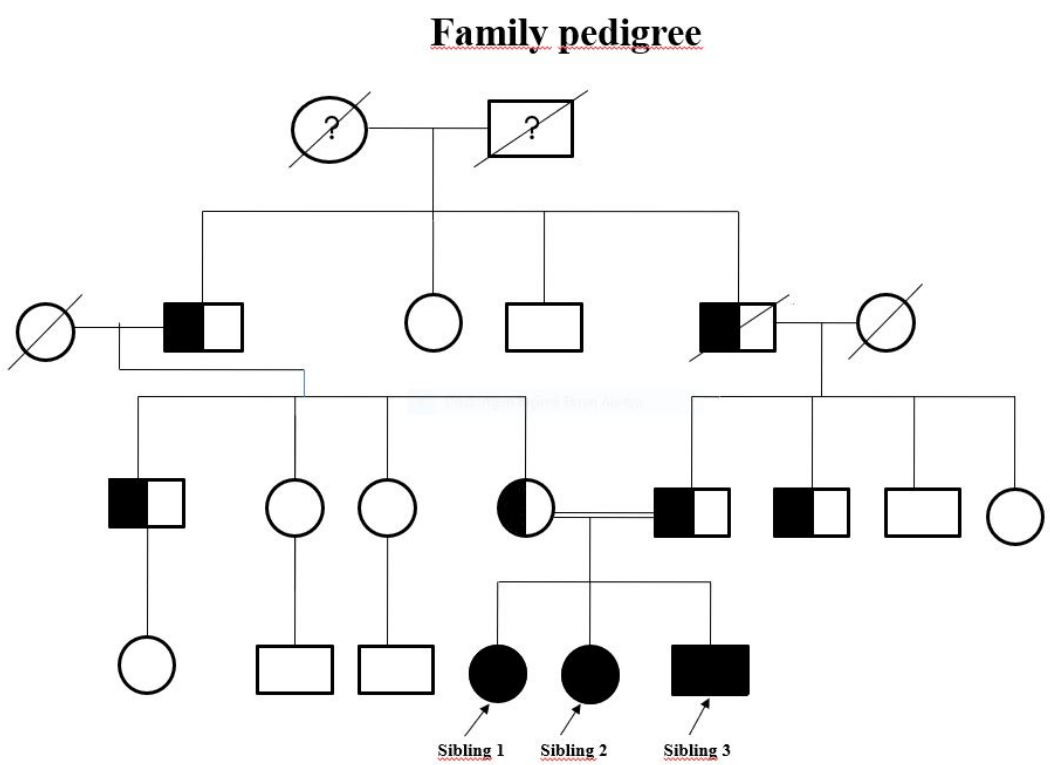

Figure 4: Pedigree of the *TMEM5* mutation family.

Gene transcript	Location	Annotation	Zygosity	Classification
RXYLT1 NM_014254.2	hg19:Chr12:64173874 exon 1 c.139del p.(Ala47Argfs*42)	Frameshift rs397514696	Homozygous	Pathogenic (PVS1, PM2, PP5)

Table 1: Genetic mutation information of all cases

Discussion:

We describe a family in which multiple members carried homozygous mutations in the *TMEM5* gene, specifically an early frameshift mutation p. Ala47Argfs*42 (c.139delG) located in exon 1. This variant was transmitted within the family and resulted in variable phenotypic outcomes. The affected individuals included one male and two female siblings. The male patient exhibited clinical features resembling MEB, whereas his two sisters displayed a more severe phenotype, also consistent with MEB, suggesting potential sex-related or individual-specific variability in disease expression. Magnetic resonance imaging (MRI) in one of the affected females demonstrated dilated ventricles and cerebellar atrophy, confirming structural involvement of the central nervous system. These findings parallel previously published data in which the identical *TMEM5* mutation was identified and associated with similar neurological abnormalities [15]. Other studies have linked *TMEM5* mutations to cobblestone lissencephaly in neonates [3], and a male patient carrying the *TMEM5* nonsense mutation p.Arg340* was reported to show clinical features consistent with WWS, leading to early death [15]. Interestingly, none of the three individuals in our study demonstrated cobblestone lissencephaly or WWS, highlighting phenotypic diversity even among patients with pathogenic variants in *TMEM5*.

Our observations further emphasize that the clinical presentation of *TMEM5*-related dystroglycanopathies can vary widely. The phenotype may range from milder forms—characterized primarily by congenital muscular dystrophy and persistently elevated creatine kinase (CK) levels without significant brain malformations—to more severe forms with pronounced brain structural abnormalities and ocular defects. This variability is consistent with previous reports documenting heterogeneity in *TMEM5*-associated disorders [16]. Collectively, our results suggest the presence of genotype–phenotype correlations in *TMEM5*-related dystroglycanopathies, where frameshift mutations may drive either severe neurological symptoms or attenuated clinical characteristics depending on modifying factors. A recent study broadened the mutational spectrum of *TMEM5* by identifying five distinct variants in five unrelated families: two missense mutations, c.1016A>G (p.Tyr339Cys) and c.1019_1020delinsTT (p.Arg340Leu), and three frameshift mutations, c.795delG (p.Glu265fs8), c.1064_1091del (p.Asp355Valfs33), and c.279delA (p.Gly94Glufs*33) [3]. Among these cases, one family presented with relatively mild cerebral dysplasia accompanied by severe retinal dysplasia, while the other four demonstrated severe cerebral involvement along with moderate retinal malformations. These findings underscore both the clinical overlap and the phenotypic variability of *TMEM5*-associated disorders.

When compared with that cohort, the three individuals in our study exhibited distinct mutant variations and clinical courses, which further

illustrates the complexity of this condition. However, due to the limited number of reported cases worldwide, definitive conclusions regarding genotype–phenotype relationships remain elusive. The rarity of *TMEM5* mutations makes it challenging to distinguish whether observed variability arises solely from the underlying mutation or whether other genetic and epigenetic modifiers are involved. Importantly, our findings highlight the value of next-generation sequencing (NGS) technologies in clinical diagnostics. Without targeted sequencing, the identification of this early frameshift mutation in exon 1 of *TMEM5* would have been difficult, particularly given the nonspecific presentation of congenital muscular dystrophy and overlapping features with other dystroglycanopathies. NGS enabled precise molecular diagnosis, thereby contributing to improved disease classification and counseling for affected families. The clinical distinctions between our patients and previously described *TMEM5* cases suggest that the pathogenic variant alone does not fully determine the phenotypic outcome. It is plausible that additional modifiers within the α-dystroglycan (α-DG) glycosylation pathway or other molecular networks influence disease severity and organ involvement. Such modifiers could account for why some individuals present only with muscular dystrophy and elevated CK, while others develop severe central nervous system or ocular malformations.

Conclusion:

This family provides further evidence of the broad phenotypic spectrum associated with *TMEM5* mutations, ranging from mild muscular presentations to severe structural brain abnormalities. The identification of the c.139delG (p.Ala47Argfs*42) mutation expands the catalog of pathogenic variants and reinforces the necessity of comprehensive genetic testing in suspected dystroglycanopathies. Larger cohorts and functional studies are essential to clarify genotype–phenotype relationships and to identify potential genetic modifiers that may explain variability in clinical outcomes.

Ethics Committee Approval

This study was approved by the Ethical Committee of Umraniye Training and Research Hospital (Ethics No: B.10.1.TKH.4.34.H.GP.0.01/12, 26/01/2023), School of Medicine, University of Health Sciences, Istanbul, Turkey.

Authors' Contributions

GH contributed to the concept of the study, acquired, analyzed, and interpreted the data, and took the lead in writing the manuscript. ME, MHY, and BK contributed to the concept of the study, collection of the data, and the interpretation of the results.

Conflicts of Interest

Metin Eser (ME), Gulam Hekimoglu (GH), Murat Hakki Yarar (MHY), and Busra Kutlubay (BK) have no conflicts of interest that are directly or indirectly related to the content of this article.

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Internet resources

ClinGen RASopathy Expert Panel (ClINGEN-RAS), ncbi.nlm.nih.gov/clinvar/submitters/ 506439/

ClinGen Inherited Cardiomyopathy Expert Panel (CMP-EP), ncbi.nlm.nih.gov/clinvar/submitters/506161/

Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), ncbi.nlm.nih.gov/clinvar/submitters/505954/

Ensembl VEP pick options. https://www.ensembl.org/info/docs/tools/vep/script/vep_other.html#pick_options

Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), ncbi.nlm.nih.gov/clinvar/submitters/504863/

Pharmacogenomics Knowledge Base, Stanford University (PharmGKB), ncbi.nlm.nih.gov/clinvar/submitters/500295/

The Clinical and Functional Translation of CFTR (CFTR2), ncbi.nlm.nih.gov/clinvar/submitters/500092/

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