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Original Research Article

Molecular Characterization of Family Presenting Autosomal Recessive Spinocerebellar Ataxia with Axonal Neuropathy

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Abstract

Autosomal recessive spinocerebellar ataxia with axonal neuropathy (ARSACS) is a neurodegenerative disorder characterized by juvenile onset of progressive cerebellar ataxia, axonal sensorimotor peripheral neuropathy, and increased serum alpha-fetoprotein. The objective of this study was to identify the molecular cause of disease in a consanguineous family from district Lakki Marwat, Khyber Pakhtunkhwa, Pakistan. A four-generation family with four affected siblings was enrolled, and whole exome sequencing was performed after ethical approval and informed consent from all family members. Clinical history was documented and blood samples were collected for DNA extraction. Whole exome sequencing revealed a previously known homozygous variant in the *SETX* gene (c.6694C>T; p.Arg2232Cys). Sanger sequencing validated the variant and confirmed autosomal recessive segregation within the family. In conclusion, this study confirms the utility of whole exome sequencing as a first-line molecular diagnostic tool in monogenic neurological disorders and underscores the importance of premarital genetic screening in consanguineous populations.

Keywords: Spinocerebellar Ataxia, Autosomal Recessive, Axonal Neuropathy, SETX Gene, Whole Exome Sequencing, Consanguinity, Molecular Diagnostics, Neurodegenerative Disorder.

INTRODUCTION

The brain is the most complex organ in the human body and consists of millions of neurons connecting different parts of the brain with each other and with body systems. It is structurally divided into the cerebrum, cerebellum, and brain stem. The cerebrum contains two hemispheres with an outer gray matter cortex and inner white matter. The cerebral cortex is subdivided into frontal, temporal, parietal, and occipital lobes, each responsible for specialized neurological functions (Lvovs *et al*., 2012).

The frontal lobe regulates personality, behavior, speech, planning, memory, movement control, and executive function. The temporal lobe is primarily associated with memory storage and retrieval, sound recognition, speech comprehension, and emotional processing. The parietal lobe integrates sensory inputs including touch, vibration, pain, temperature, and spatial recognition (Jackson *et al*., 2018). The occipital lobe is responsible for visual interpretation and processing. Damage to these lobes results in neurological deficits such as aphasia, apraxia, sensory loss, visual defects, emotional dysregulation, and impaired cognition (Griffiths *et al*., 2012).

Genetic disorders arise from abnormalities in genes or chromosomes and may be monogenic, polygenic, or chromosomal in origin. Inheritance patterns include autosomal recessive, autosomal dominant, X-linked dominant, and X-linked recessive transmission. Approximately 6000 genetic disorders have been described, most of which are rare and often associated with neurological dysfunction (Paulson *et al*., 2017).

Ataxia is a neurological disorder characterized by abnormal coordination of voluntary muscle movements due to dysfunction of the cerebellum or sensory pathways. It may be acquired or hereditary (Alonso *et al*., 2013). Among hereditary forms, spinocerebellar ataxias (SCAs) are a group of progressive neurodegenerative disorders, mostly inherited in an autosomal dominant pattern. More than 30 types of SCAs have been identified, including SCA1, SCA2, SCA3, SCA6, and SCA7. Many of these are

caused by CAG trinucleotide repeat expansions in genes encoding ataxin proteins, leading to toxic polyglutamine accumulation and neuronal degeneration (Ruano *et al*., 2014).

Spinocerebellar ataxias represent a genetically heterogeneous group of progressive neurodegenerative disorders characterized by cerebellar atrophy, gait disturbance, dysarthria, cognitive impairment, and visual abnormalities (Barnard *et al*., 1971). Despite identification of multiple causative genes, the molecular mechanisms underlying neuronal degeneration remain incompletely understood. Clinical overlap among different SCA types complicates diagnosis, prognosis, and genetic counselling. Furthermore, anticipation due to CAG repeat expansion results in earlier onset and increased severity in successive generations, increasing disease burden within affected families (Boor & Hurtig, 1977).

Understanding cerebral physiology and the genetic mechanisms of spinocerebellar ataxias is essential for accurate diagnosis, early detection, and effective genetic counselling. Identification of specific gene mutations such as ATXN1, ATXN2, ATXN3, and CACNA1A improves molecular classification and supports precision medicine approaches (Jen *et al*., 2007). Knowledge of inheritance patterns assists families in risk assessment and reproductive decision-making. Additionally, understanding the pathophysiology of polyglutamine-mediated neurodegeneration contributes to the development of targeted therapeutic strategies (Jackson *et al*., 1977).

Although several SCA subtypes have been genetically characterized, variability in clinical presentation and progression indicates underlying molecular complexity (Velázquez-Pérez *et al*., 2011). Expanded CAG repeats produce toxic ataxin proteins that accumulate in Purkinje cells, disrupting the ubiquitin-proteasome pathway and leading to neuronal degeneration. However, genotype-phenotype correlations remain inconsistent. A structured review of cerebral function, inheritance patterns, and molecular mechanisms provides a comprehensive understanding necessary for improving diagnostic accuracy and future therapeutic interventions (Maruff *et al*., 1996).

Despite the identification of more than 30 SCA subtypes, limited data exist regarding precise molecular pathways linking CAG repeat expansion to selective cerebellar vulnerability. There is insufficient integration of cerebral lobe dysfunction with genetic mutation profiles in many studies. Additionally, overlapping phenotypes among different SCA types hinder early differentiation, particularly in resource-limited settings. Further research is required to clarify genotype-phenotype relationships, identify biomarkers for early detection, and explore disease-modifying therapeutic targets. The present study aims to provide molecular characterization of a consanguineous family presenting with autosomal recessive spinocerebellar ataxia with axonal neuropathy, thereby contributing to the growing knowledge base on SETX-associated disorders.

EXPERIMENTAL SECTION / MATERIALS AND METHODS

Ethical Approval

Under reference number 529/ORIC/ICP, the institutional Bioethical Committee approved this research involving human DNA samples. All eight patients enrolled in the research family were above 18 years of age and voluntarily signed a consent form designed according to national bioethical research rules. For affected participants who were unable to interpret the consent form, consent was provided by their legal guardians. The guidelines of the Declaration of Helsinki 2013 were followed throughout the research to maintain biosafety measures and uphold human rights.

Study Design and Setting

This was a family-based molecular diagnostic study. A four-generation consanguineous family from district Lakki Marwat, Khyber Pakhtunkhwa, Pakistan was enrolled. The study was conducted at the Department of Medical Laboratory Technology, Northwest Institute of Health Sciences, Peshawar.

Sample Collection

Eight family members were enrolled in the study. Peripheral blood (5 ml) was collected from each participant in EDTA tubes, which were properly labelled with sequence numbers and participant names. Phlebotomy and sample transport were conducted according to national guidelines. Samples were stored for two days in a refrigerator at 6°C prior to DNA extraction.

DNA Extraction

Genomic DNA was extracted using the organic phenol-chloroform method. Briefly, 750 µl of blood was transferred to a 1.5 ml microcentrifuge tube, and 750 µl of Solution A was added with thorough mixing. The mixture was incubated at room temperature for 5-10 minutes, followed by centrifugation at 13,000 rpm for 1 minute. The supernatant was discarded and the wash step was repeated. Solution B (400 µl), 12 µl of 20% SDS, and 5 µl of proteinase K were added and incubated overnight at 37°C. The following day, Solutions C and D (250 µl each) were added, followed by centrifugation at 13,000 rpm for 10 minutes. The upper aqueous phase was transferred to new tubes, and 500 µl of Solution D was added with re-centrifugation. The aqueous phase was combined with 55 µl of 3M sodium acetate and 500 µl of cold isopropanol, inverted to visualize DNA threads, and centrifuged for 10 minutes. The DNA pellet was washed with 200 µl of 70% ethanol, dried, and resuspended in 200 µl of Tris-EDTA buffer overnight at 37°C.

Quantification of Genomic DNA

Extracted DNA was quantified using a NanoDrop™ spectrophotometer. One microlitre of each sample was used to determine purity (A260/A280 ratio) and concentration.

Gel Electrophoresis

The presence and integrity of extracted DNA was confirmed by agarose gel electrophoresis using an electric field to separate DNA fragments by size. Bands were visualized under ultraviolet (UV) light.

Whole Exome Sequencing

Whole exome sequencing (WES) was performed by Macrogen, Republic of Korea, to identify disease-causing variants. The workflow included: (1) DNA extraction from whole blood; (2) DNA fragmentation; (3) binding of fragments; (4) aqueous phase hybridization; (5) sequencing of exonic regions by next-generation sequencing (NGS); and (6) in silico alignment to the human genome reference sequence. The sequencing results were analyzed for pathogenic variants following the autosomal recessive model of inheritance.

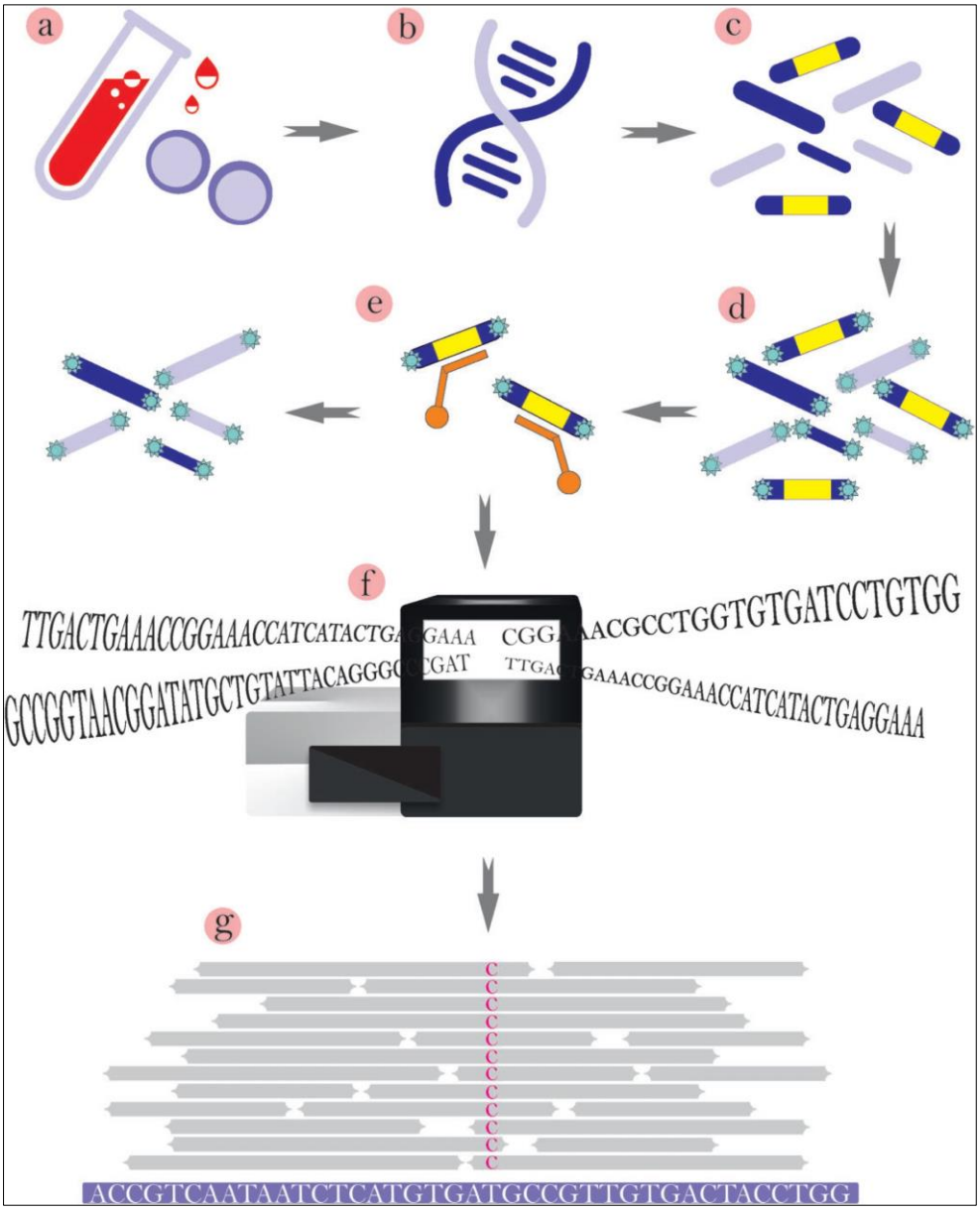

Figure 1: Path flow of Whole Exome Sequencing

Sanger Sequencing and Primer Design

Candidate variants identified by WES were validated by Sanger sequencing to confirm pathogenicity and Mendelian segregation. PCR amplification was performed for relevant exons, and products were separated by gel electrophoresis prior to sequencing. Primers for the SETX gene (exon 21) were designed using Primer3Plus software:

Forward primer (SETX_1F): 5'-CTGGAAAGATCCGAGTGACG-3'

Reverse primer (SETX_1R): 5'-ATGGACTGTCCGACTTTGCT-3'

The PCR product size was 376 bp. PCR reactions were performed using Taq DNA polymerase (50 units/ml), dNTPs (400 µM each), and $MgCl_2$ (3 mM) in a 50 µl reaction volume. PCR products were purified using the PureLink kit by bind-wash-elute procedure and diluted in TE buffer before sequencing. Bidirectional sequencing was performed using both forward and reverse primers for comprehensive variant identification.

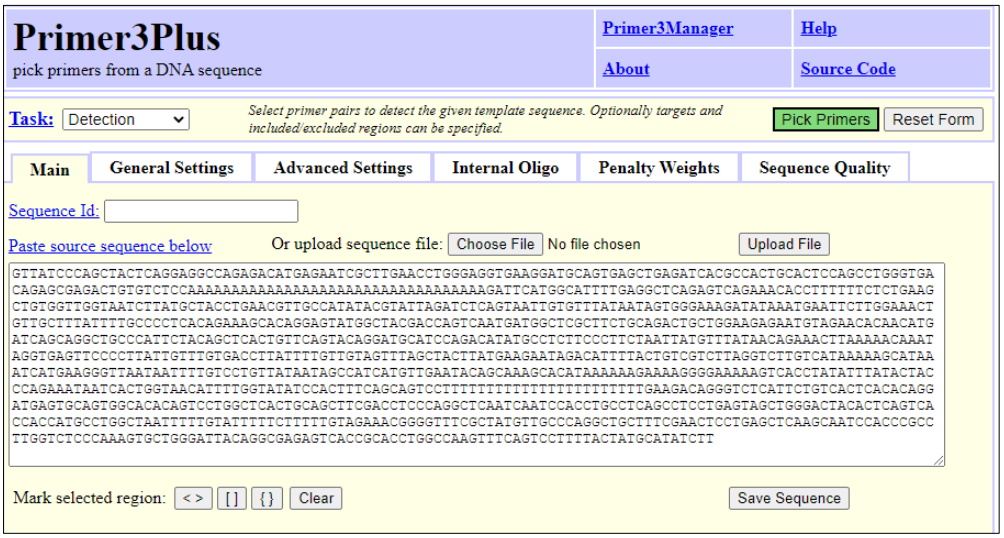

Figure 2: Main dialogue box in Primer3Plus software showing the FASTA sequence input window used for primer design

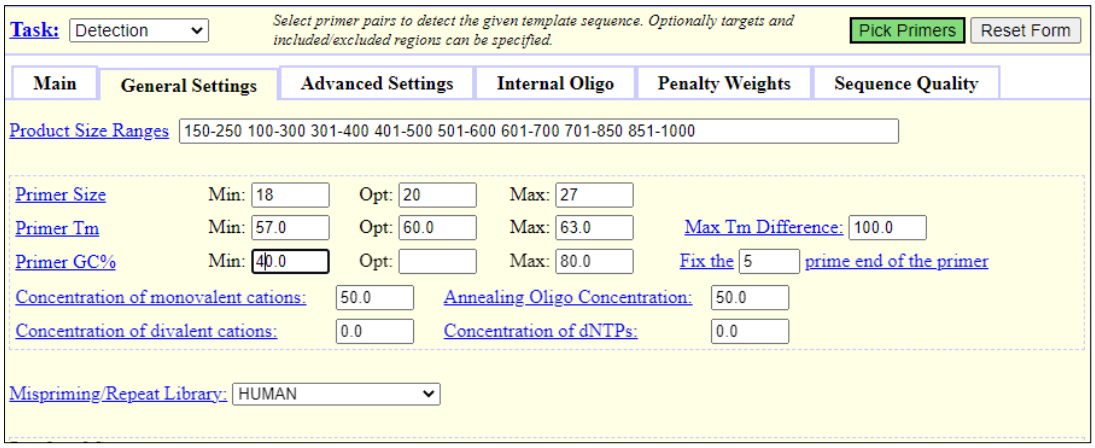

Figure 3: Primer3Plus output showing primer design parameters for SETX exon 21

Variant Analysis

Shortlisted variants were filtered based on: (a) minor allele frequency (MAF) below 0.001; (b) exonic location; (c) predicted pathogenicity using MutationTaster (https://www.mutationtaster.org/); and (d) homozygous or compound heterozygous state. Variants were verified in population-based databases including the Genome Aggregation Database (gnomAD) and ClinVar. Prediction tools including SIFT, PolyPhen-2, and MutationTaster were used to assess the functional impact of amino acid changes on the encoded protein.

RESULTS AND DISCUSSION

Patient History

The research family originated from Lakki Marwat, Khyber Pakhtunkhwa, Pakistan. Detailed patient and family history were obtained from family elders for this four-generation pedigree. The family had a history of consanguineous marriages across multiple generations, with two first-cousin marriages identified. At the time of the study, only female siblings were present in the fourth generation, of whom four were affected.

The eldest affected sibling (IV-3), aged 35, developed inability to walk and maintain balance after completing her A-levels. Progressive loss of ambulation occurred gradually, leading to complete dependence on support for standing and walking. Early clinical assessment had suggested spinocerebellar ataxia. Prior treatment interventions were discontinued due to lack of improvement. At the time of the latest visit, she exhibited shaky and jerky body movements, nystagmus, inability to focus for reading, and dependence for routine

activities. Despite loss of ambulation and ataxia, she retained excellent conversational skills and good understanding of her disease history.

Siblings IV-4 and IV-5, aged 27 and 24 years respectively, had a similar disease progression history. Sibling IV-6, aged 12, had not yet developed phenotypic features, as the age of onset in the family was consistently above 18 years. All affected patients presented with food and water swallowing difficulties. Complete blood count revealed lymphocytopenia with increased platelet counts. Complaints of lower limb numbness, hypermuscle contractions, and tremors consistent with polyneuropathy were documented. Sensory function was intact but responses were mildly slowed.

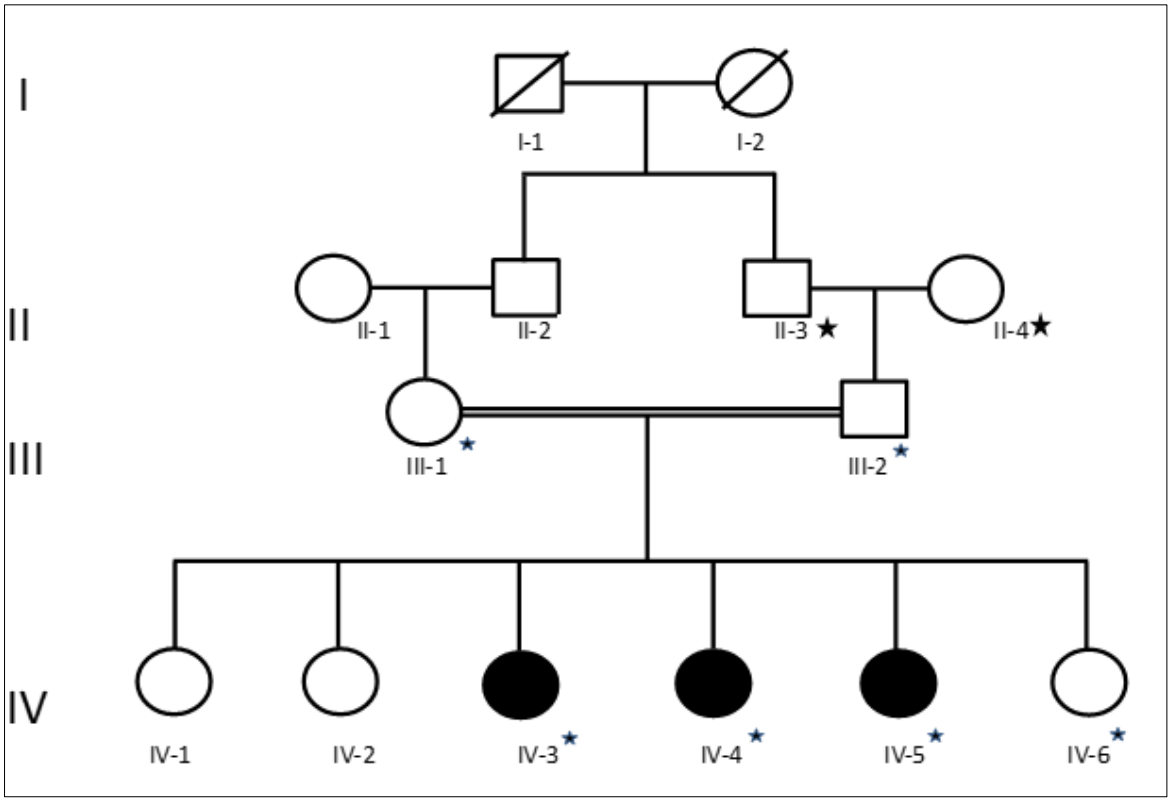

Figure 4: Four-generation pedigree of the study family. Squares represent males; circles represent females. Filled figures indicate affected members. The cross symbol indicates deceased individuals. Three affected and three unaffected siblings are present in the fourth generation. The pedigree demonstrates an autosomal recessive pattern of inheritance

Molecular Diagnosis

Following the autosomal recessive inheritance model, WES analysis filtered variants with: (a) MAF below 0.001; (b) exonic location; (c) predicted pathogenicity; and (d) homozygous or compound heterozygous state. Two homozygous variants were shortlisted: *SETX* (NM_015046.7; c.6694C>T; NP_055861.3; p.Arg2232Cys) and *GNRHR* (NM_000406.3; c.317A>G; NP_000397.1; p.Gln106Arg).

Sanger validation confirmed autosomal recessive inheritance for the *SETX* variant (NM_015046.7; c.6694C>T), while the *GNRHR* variant did not follow Mendelian segregation for the disease phenotype. Although both variants were predicted as pathogenic by MutationTaster, only the *SETX* gene was considered causative due to its confirmed autosomal recessive segregation within the family.

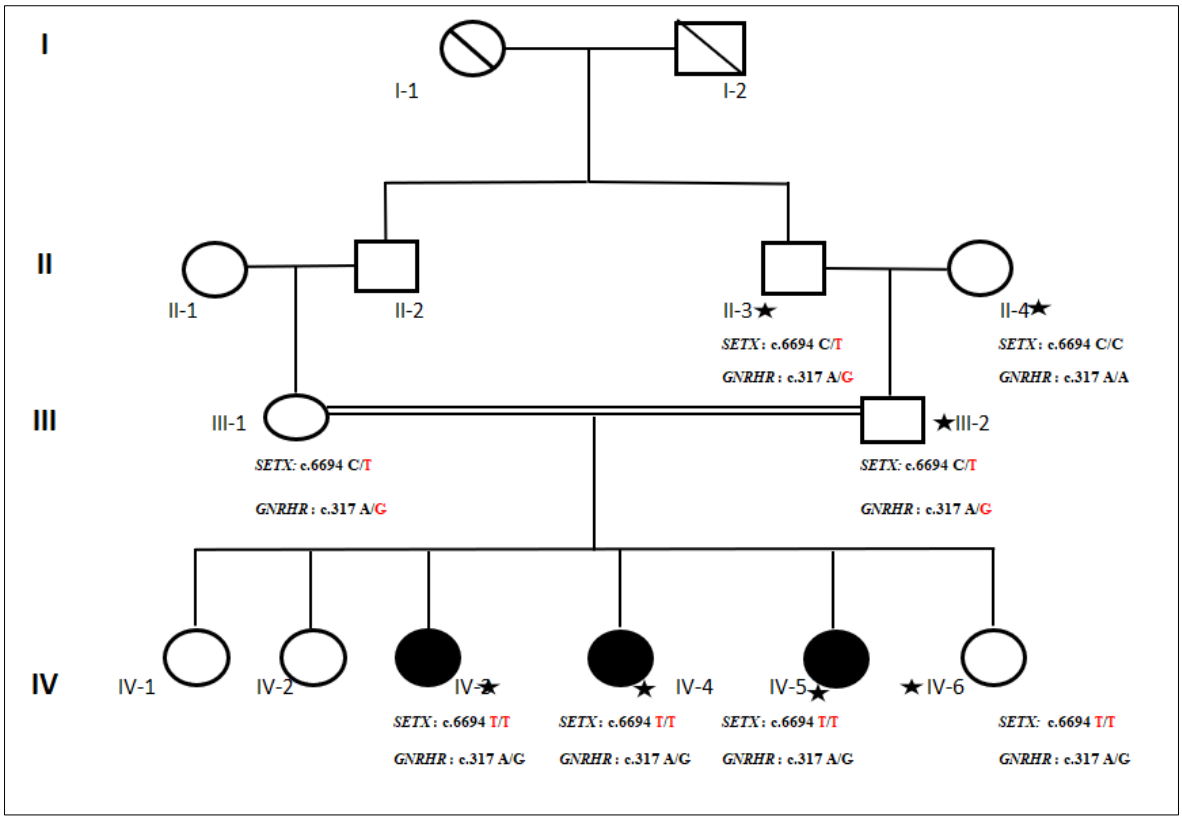

Figure 5: Pedigree showing the genotype of family members for the SETX variant

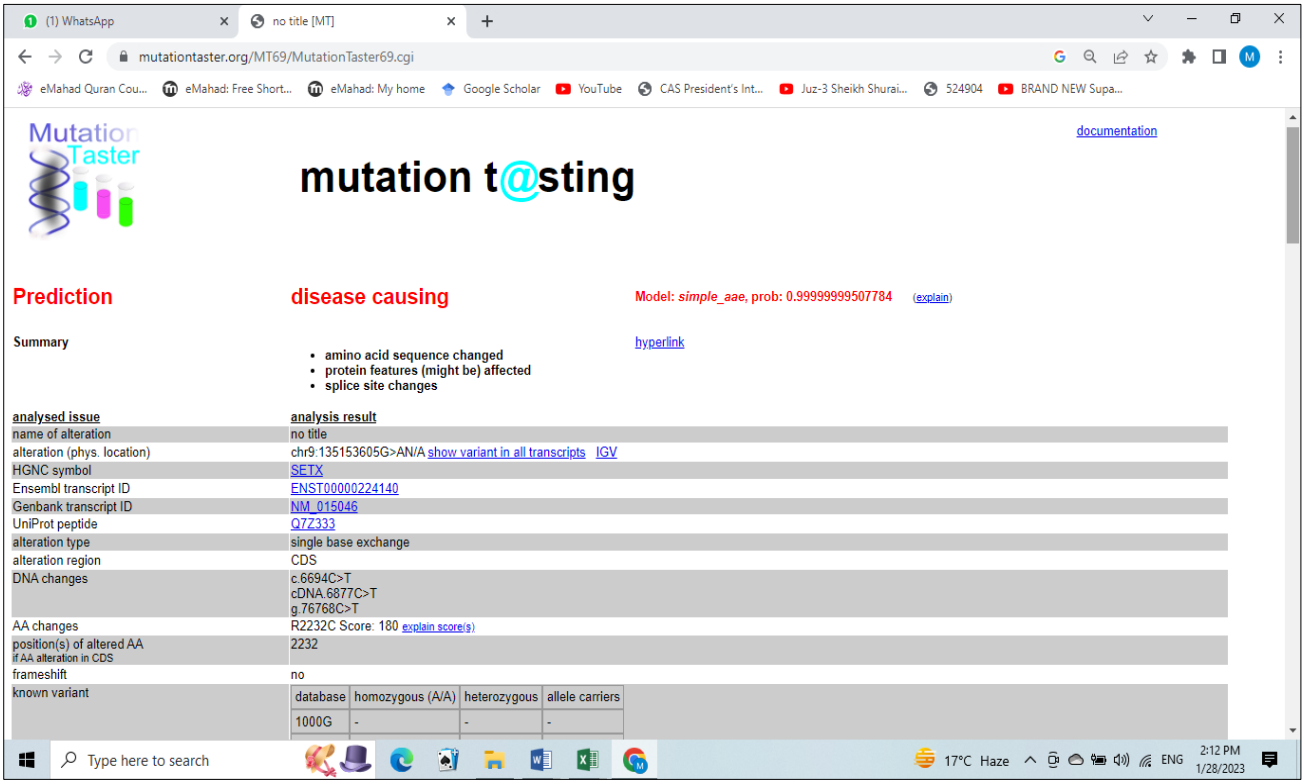

Figure 6: MutationTaster prediction output for the SETX variant (c.6694C>T)

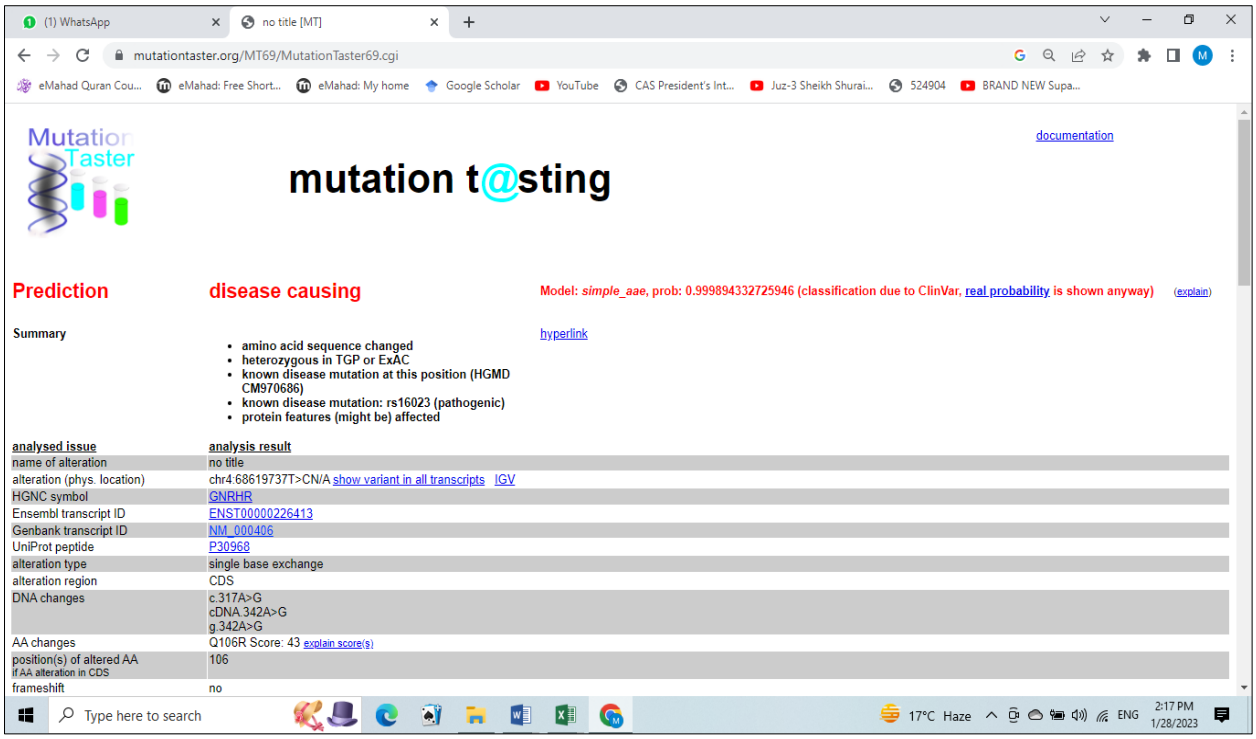

Figure 7: MutationTaster prediction output for the SETX variant showing disease-causing classification

Variant Description in Databases

GnomAD Database: The identified variants from whole exome sequencing were verified in population genomic databases. The Genome Aggregation Database (gnomAD) confirmed the allele frequency of the causative variant as 0.000003978, indicating extreme rarity in the general population.

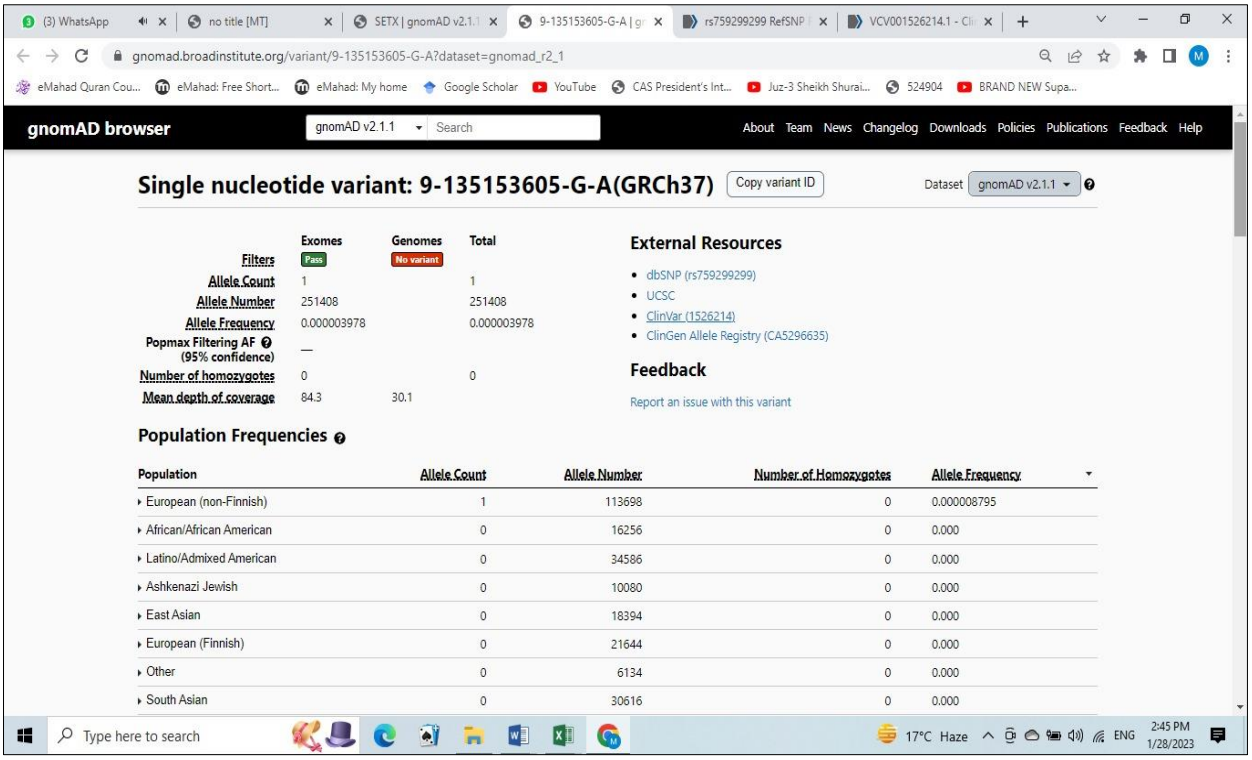

Figure 8: gnomAD database output showing the allele frequency of the SETX variant (c.6694C>T)

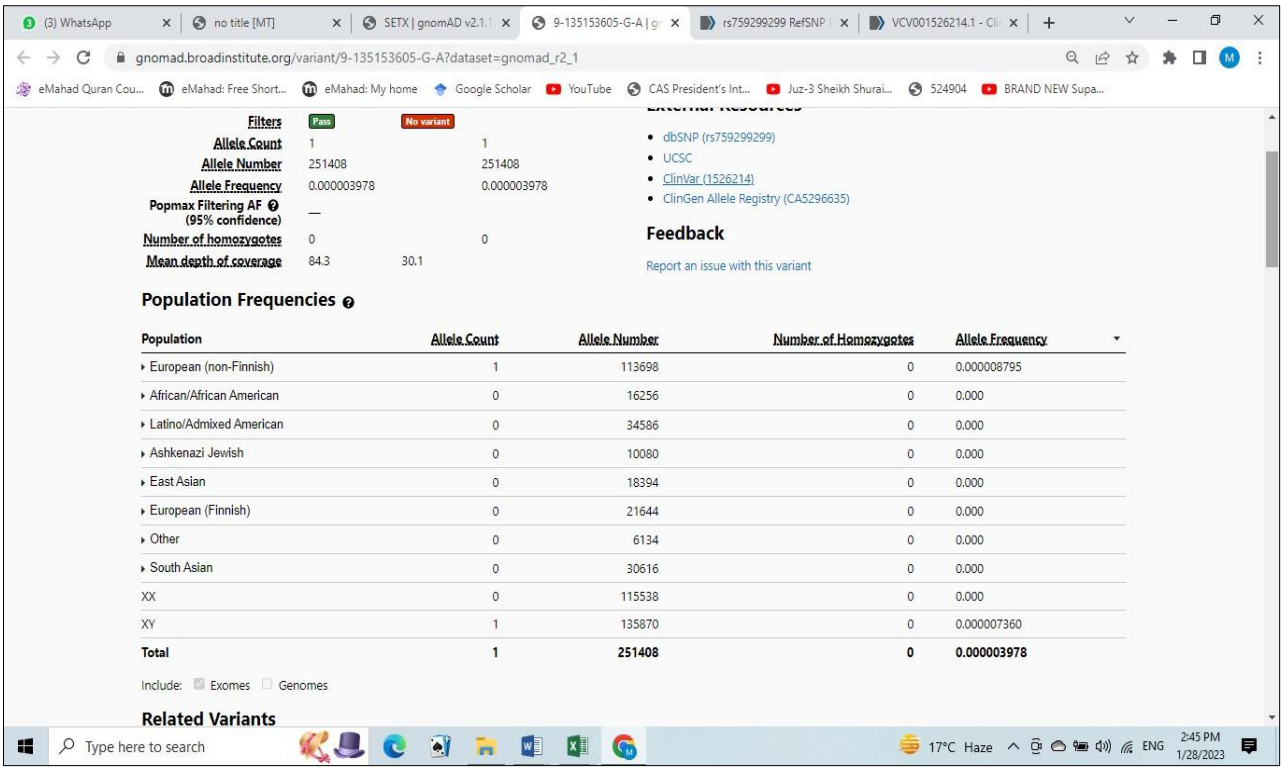

Figure 9: Detailed allele frequency data for the SETX variant from the gnomAD database.

ClinVar and dbSNP Database: ClinVar classified the identified variant as "likely pathogenic" with accession number RCV002052234.1. The dbSNP database corroborated this classification, also reporting the variant as likely pathogenic.

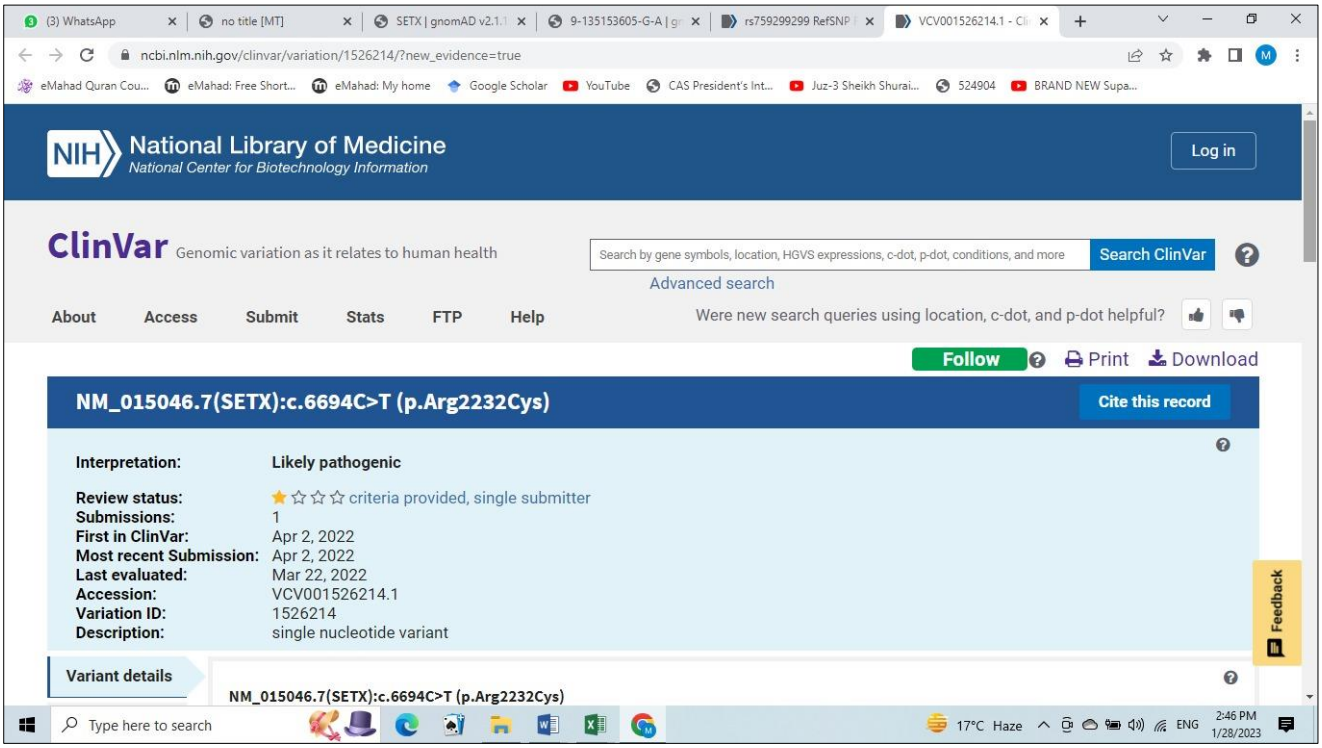

Figure 10: ClinVar database entry showing clinical significance of the SETX variant (Accession: RCV002052234.1)

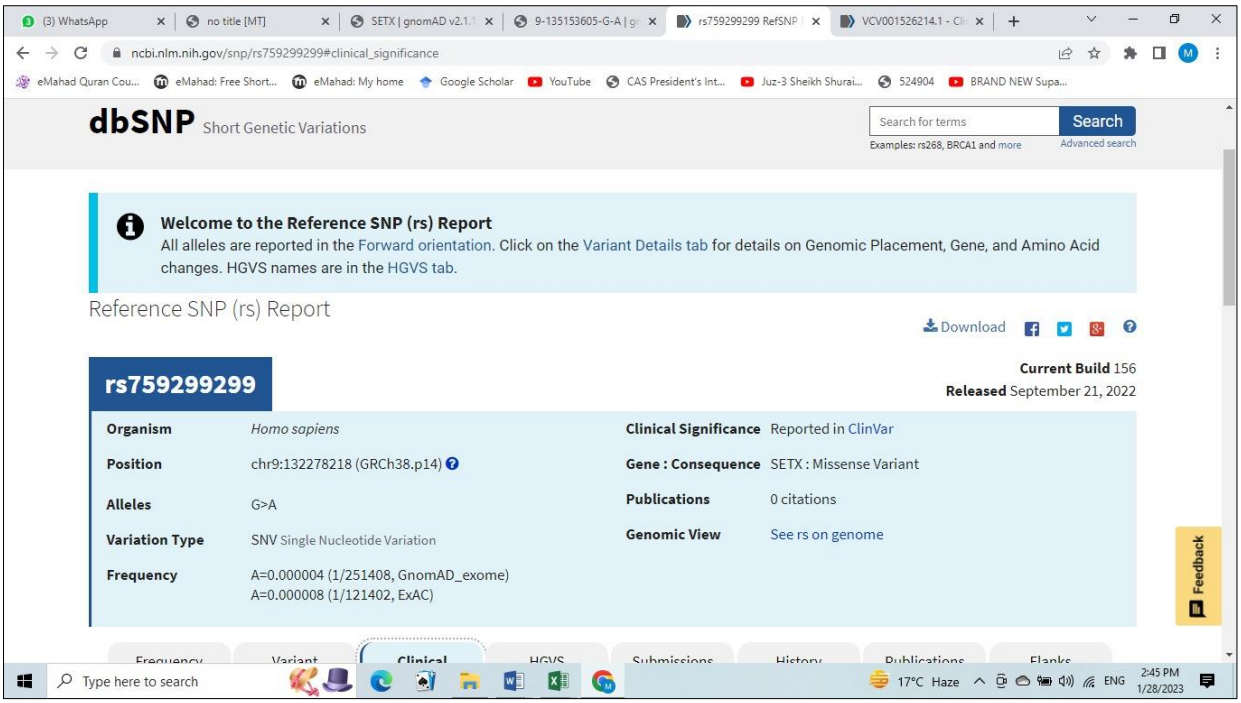

Figure 11: dbSNP database entry confirming the SETX gene variant as likely pathogenic

Table 1: Details of family members included in this study for the SETX variant

Sample No.	Condition	Relation	Sex	Age (Years)	Variant and genotype
II-1	Normal	Grandmother	Female	81	SETX: c.6694C/C Homozygous
II-2	Normal	Grandfather	Male	83	SETX: c.6694C/T Heterozygous
III-1	Normal	Father	Male	56	SETX: c.6694C/T Heterozygous
III-2	Normal	Mother	Female	55	SETX: c.6694C/C
IV-3	Affected	Daughter	Female	36	SETX: c.6694T/T
IV-4	Affected	Daughter	Female	32	SETX: c.6694T/T Homozygous
IV-5	Affected	Daughter	Female	25	SETX: c.6694T/T Homozygous
IV-6	Normal	Daughter	Female	12	SETX: c.6694T/T Homozygous

Table 2: Details of family members included in this study for the GNRHR variant.

ID	Phenotype	Relation	Sex	Age	Variant and genotype
II-1	Normal	Grandmother	Female	81y	GNRHR: c.317A/A Homozygous
II-2	Normal	Grandfather	Male	83y	GNRHR: c.317A/A Heterozygous
III-1	Normal	Father	Male	56y	GNRHR: c.317A/G Heterozygous
III-2	Normal	Mother	Female	55y	GNRHR: c.317 A/A Heterozygous
IV-3	Affected	Daughter	Female	36y	GNRHR: c.317 A/G Homozygous
IV-4	Affected	Daughter	Female	32y	GNRHR: c.317 A/G Homozygous
IV-5	Affected	Daughter	Female	25y	GNRHR: c.317 A/G Homozygous
IV-6	Normal	Daughter	Female	12y	GNRHR: c.317 A/G Homozygous

Sanger Sequencing Results – SETX Gene (Exon 21)

Multiple sequence alignment of Sanger sequencing data confirmed the location of the C>T mutation at position 6694 of exon 21 of the SETX gene relative to the reference sequence, using the BioEdit tool. This mutation results in a substitution of arginine (R) with cysteine (C) at amino acid position 2232.

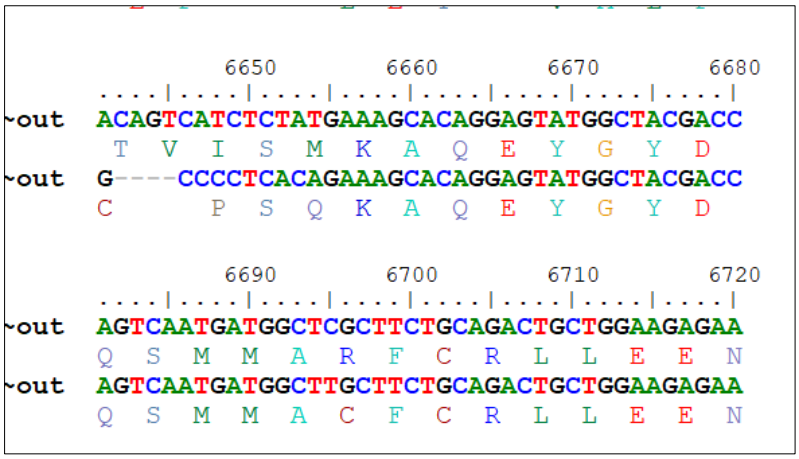

Figure 12: Multiple sequence alignment of Sanger sequencing data showing the location of mutation at position 6694 (C>T) in exon 21 of the SETX gene. The mutation changes Arginine (R) to Cysteine (C) at amino acid position 2232

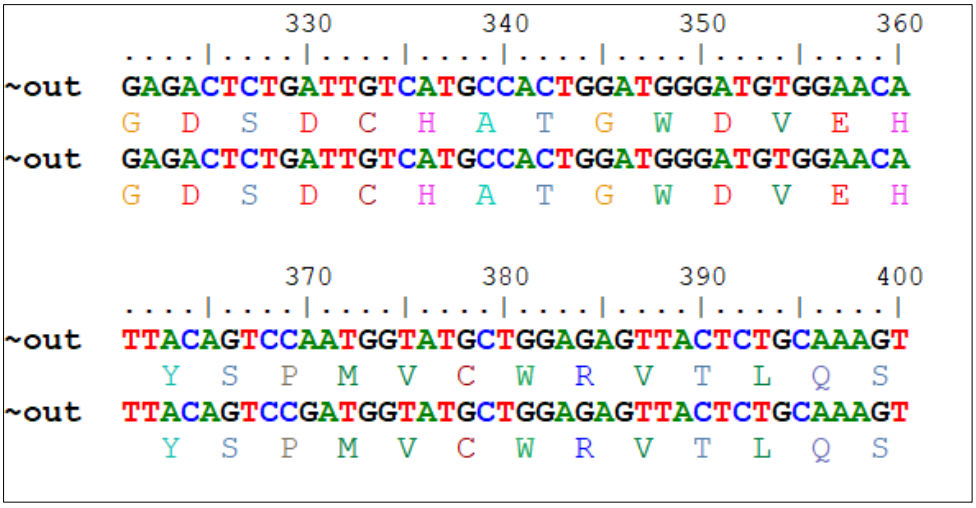

Figure 13: BioEdit multiple sequence alignment showing the GNRHR variant (c.317A>G) in exon 1. This mutation does not result in an amino acid change

Individual Sanger sequencing results for the complete exon 21 of the SETX gene (generated using the forward primer) are shown below for each family member:

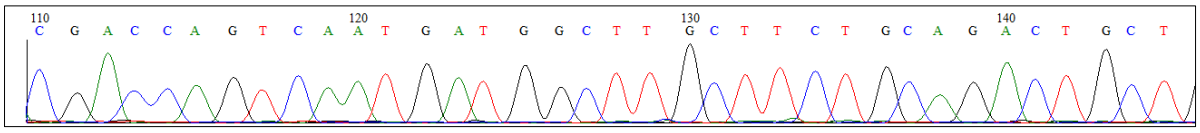

Figure 14: Sanger sequencing result of exon 21 of SETX gene in affected sibling IV-4 (forward primer)

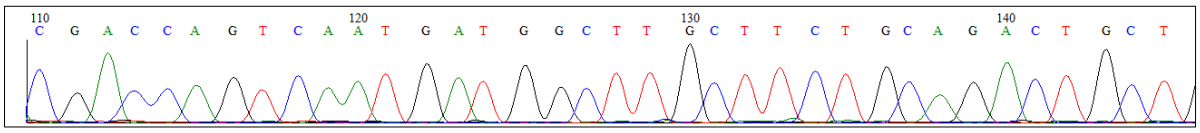

Figure 15: Sanger sequencing result of exon 21 of SETX gene in affected sibling IV-5 (forward primer)

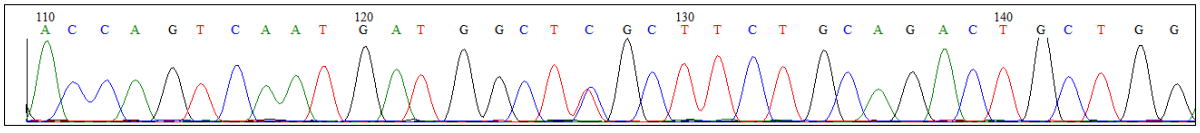

Figure 16: Sanger sequencing result of exon 21 of SETX gene in unaffected/carrier sibling IV-6 (forward primer)

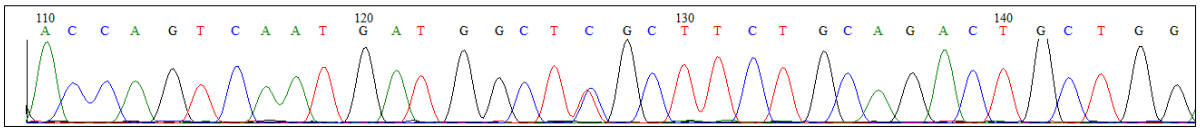

Figure 17: Sanger sequencing result of exon 21 of SETX gene in unaffected/carrier member II-1 (forward primer)

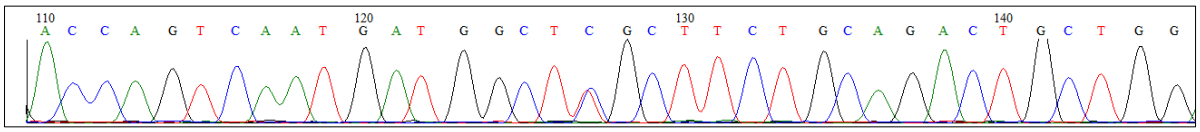

Figure 18: Sanger sequencing result of exon 21 of SETX gene in unaffected/carrier sibling II-2 (forward primer)

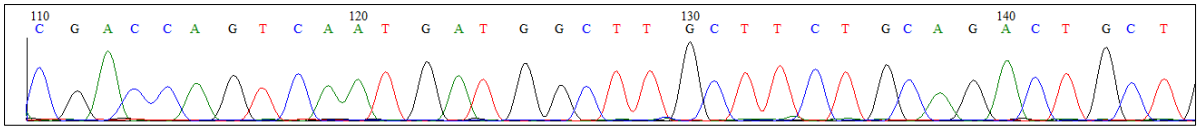

Figure 19: Sanger sequencing result of exon 21 of SETX gene in affected sibling IV-3 (forward primer)

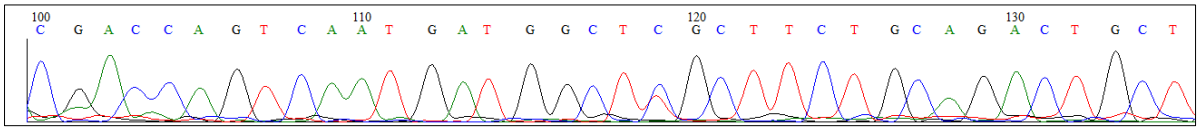

Figure 20: Sanger sequencing result of exon 21 of SETX gene in unaffected/carrier sibling III-1 (forward primer)

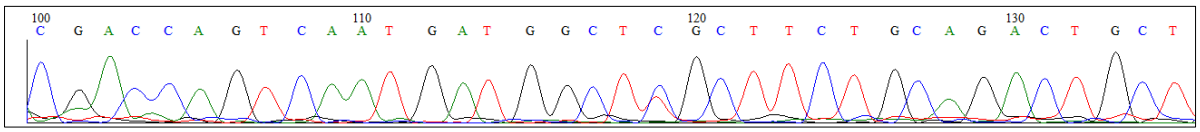

Figure 21: Sanger sequencing result of exon 21 of SETX gene in unaffected/carrier sibling III-2 (forward primer)

Sanger Sequencing Results – GNRHR Gene (Exon 1)

Individual Sanger sequencing results for the complete exon 1 of the GNRHR gene (generated using the forward primer) are shown below for each family member:

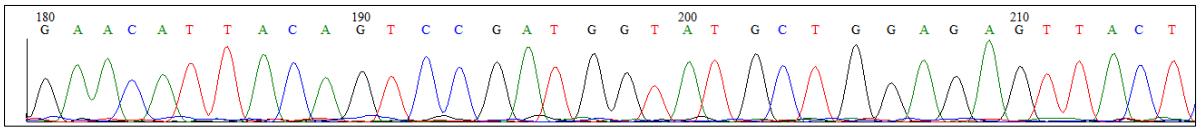

Figure 22: Sanger sequencing result of exon 1 of GNRHR gene in affected sibling IV-4 (forward primer)

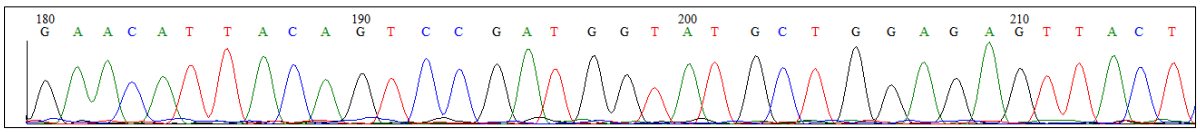

Figure 23: Sanger sequencing result of exon 1 of GNRHR gene in affected sibling IV-5 (forward primer)

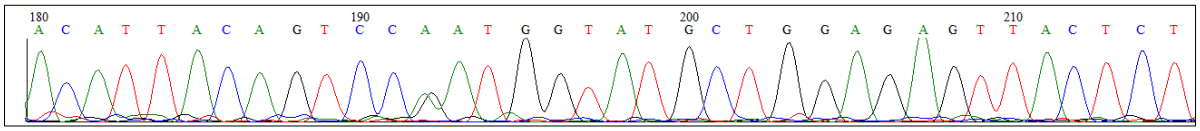

Figure 24: Sanger sequencing result of exon 1 of GNRHR gene in unaffected/carrier sibling IV-6 (forward primer)

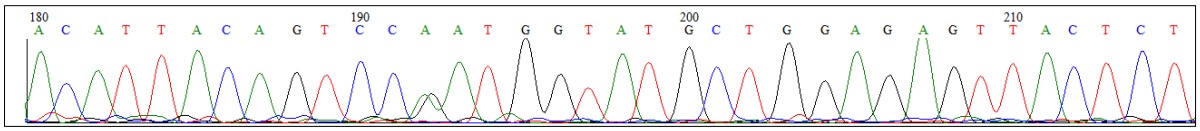

Figure 25: Sanger sequencing result of exon 1 of GNRHR gene in unaffected/carrier sibling II-1 (forward primer)

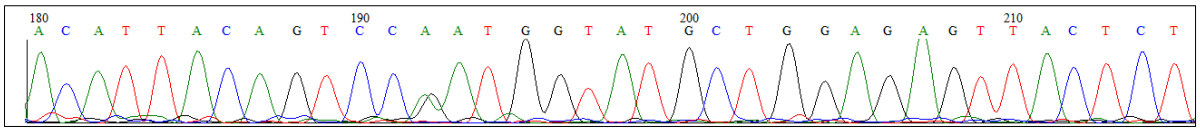

Figure 26: Sanger sequencing result of exon 1 of GNRHR gene in unaffected/carrier sibling II-2 (forward primer)

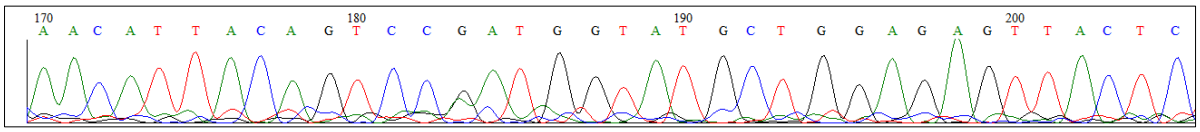

Figure 27: Sanger sequencing result of exon 1 of GNRHR gene in affected sibling IV-3 (forward primer)

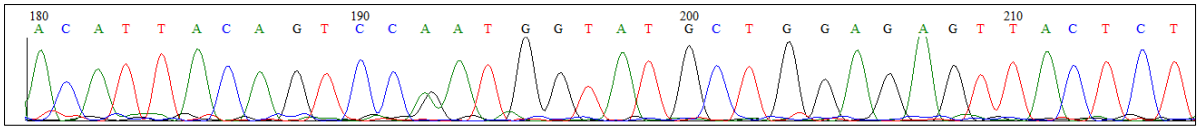

Figure 28: Sanger sequencing result of exon 1 of GNRHR gene in unaffected/carrier sibling III-1 (forward primer)

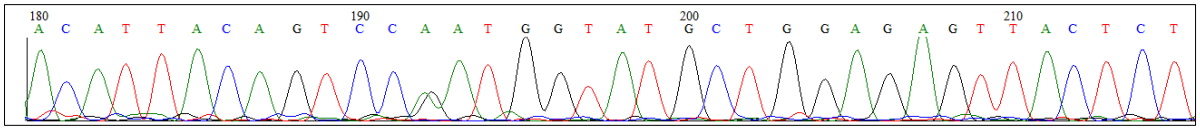

Figure 29: Sanger sequencing result of exon 1 of GNRHR gene in unaffected/carrier sibling III-2 (forward primer)

DISCUSSION

The homozygous variant c.6694C>T in the *SETX* gene had previously been reported in a European family (Edener *et al*., 2011). The primary clinical diagnosis of cerebellar ataxia with ocular apraxia in our patients was confirmed when genetic testing identified the *SETX* variant. Disease onset in our patients occurred in the late teenage years, suggesting that complete phenotype may not develop when patients are tested in early childhood. Sibling IV-6, aged 12, was classified as unaffected at the time of the study despite being homozygous for c.6694C>T (Dick *et al*., 2012). This is consistent with the pattern observed in her elder sisters, all of whom developed phenotypic features after 18 years of age (Mosemiller *et al*., 2003).

A study by (Herman-Bert *et al*., 2000) analyzed 140 genes associated with hereditary cerebellar ataxia, including both dominant and recessive patterns. Among recessive forms, *SETX* was identified as a causative gene, which is consistent with our findings. In that cohort, 44% of patients had disease onset before 25 years. The leading pathogenic variant for recessive spinocerebellar ataxia was in the *SPG7* gene (14 patients), followed by *SACS* (8 patients) and *SETX* (7 patients). Clinical features observed in our study were largely consistent with those reported by (Namekawa *et al*., 2015), with the exception that *APTX* gene variant patients showed elevated alpha-fetoprotein levels, which was not assessed in our study.

Clinical features associated with *SETX* gene variations include ataxia-ocular apraxia type 2, amyotrophic lateral sclerosis, ataxia with neuropathy, peripheral neuropathy, Charcot-Marie-Tooth disease type 2, nystagmus, slurred speech, dysmetria, dysdiadochokinesia, and reduced reflexes. However, not all features manifest in every patient (Giuffrida *et al*., 1999). In our patients, nystagmus and progressive loss of ambulation developed gradually. Biochemical investigations such as serum alpha-fetoprotein and MRI of the central and peripheral nervous systems could not be performed in all patients, limiting comprehensive genotype-phenotype correlation for *SETX*-associated disease (Chen *et al*., 2022).

The *SETX* gene is located on chromosome 9q34.13. It contains 26 exons, of which 24 are coding, beginning at exon 3 and ending at exon 26. The gene encodes senataxin, a DNA/RNA helicase protein of 302.8 kDa containing 2677 amino acids. The gene was first identified and named in 2004 due to its high similarity with the fungal sen1p gene. The disease-causing variant identified in our study is located in exon 21, which is 188 nucleotides long and encodes 63 amino acids. Three missense variants have previously been reported in exon 21 (Paucar *et al*., 2019).

The *SETX* gene functions in DNA repair, RNA processing, and transcription termination (Anheim *et al*., 2009). It regulates gene expression by inhibiting RNA polymerase II binding at promoter regions and resolves R-loops to reduce DNA damage. Recent evidence also implicates *SETX* in promoting autophagy and clearance of ubiquitinated proteins in the cytoplasm. Cells with reduced *SETX* function show significantly diminished autophagy activity, with ubiquitinated protein

accumulation approximately six times higher than in normal cells (Coutelier *et al*., 2018).

SETX mutations primarily cause two types of neurological disorders: (a) autosomal recessive cerebellar ataxia, and (b) autosomal dominant amyotrophic lateral sclerosis. A third disorder type associated with impaired autophagy may also be linked to *SETX* alterations. In neurological disease, accumulation of ubiquitinated proteins causes DNA damage, and reduced autophagy in glial cells promotes neurodegeneration. Autophagy-related gene variants have previously been identified in the Pakhtun population, and their recurrence in future generations of affected families cannot be excluded (Nanetti *et al*., 2013).

CONCLUSION

This study confirms the molecular diagnosis of a consanguineous family from Khyber Pakhtunkhwa, Pakistan presenting with autosomal recessive spinocerebellar ataxia with axonal neuropathy. Whole exome sequencing identified a known homozygous pathogenic variant in the *SETX* gene (c.6694C>T; p.Arg2232Cys), which was validated by Sanger sequencing and confirmed to segregate in an autosomal recessive pattern within the family. These findings underscore the clinical utility of WES as a first-line molecular diagnostic approach for rare monogenic neurological disorders. Premarital genetic screening and molecular carrier testing should be encouraged in consanguineous communities to reduce the burden of heritable neurological diseases. Expanding such initiatives in resource-limited settings is essential for early diagnosis, genetic counseling, and informed reproductive decision-making.

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