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Original Article

Genetic Homogeneity of a *TDP1* Variant, c.1478A>G, as the Main Disease-Causing Variant of Spinocerebellar Ataxia With Axonal Neuropathy 1 (SCAN1) in the Middle East: A Systematic Review

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ABSTRACT

Background: Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) is an ultrarare neurodegenerative disorder inherited in an autosomal recessive manner, mainly marked by progressive ataxia and axonal polyneuropathy. SCAN1 is mainly caused by the c.1478A>G:p.His493Arg mutation in the *TDP1* gene. In this study, we present the first Iranian family, and the fifth family totally, diagnosed with the SCAN1, which carries the common variant c.1478A>G. Additionally, we conducted a systematic review to identify all reported probably disease-related variants of *TDP1*.

Methods: Whole exome sequencing was performed on the proband, who was initially diagnosed with axonal neuropathy. The data were analyzed, and the variant was confirmed via Sanger sequencing. Cosegregation analysis was used to validate the variant within the family. Following PRISMA 2020 guidelines, we performed a systematic review using the terms *TDP1*, tyrosyl-DNA phosphodiesterase, SCAN1, and spinocerebellar ataxia with axonal neuropathy in four major databases.

Results: Whole exome sequencing results identified the known *TDP1*:c.1478A>G variant, which correlated with the disease status in the family. Clinical and paraclinical findings were consistent with SCAN1. Our systematic review identified 16 variants in 20 families associated with various neurological or non-neurological disorders. Among these families, four were SCAN1. Although four of five families with SCAN1, including our family, shared the same *TDP1* variant, c.1478A>G, they exhibited some clinical heterogeneity.

Conclusions: Given that all these cases were from the Middle East, we suggested this mutation may be a founder mutation in this region. Since only a few families with SCAN1 have been reported, further research is needed to fully understand this disorder.

Introduction

The *TDP1* gene (OMIM:607198), located on chromosome 14q32.11 and containing 17 exons, encodes tyrosyl-DNA phosphodiesterase 1, a 608-amino acid protein. This protein has two main domains: a 148-amino acid regulatory domain at the N terminus and a catalytic domain at the C terminus.[1-3] TDP1 plays a role in various DNA repair pathways, particularly in repairing single-strand breaks caused by the enzyme topoisomerase I (TOPI). TOPI regulates DNA topology by forming covalent bonds with DNA, resulting in reversible TOPI-DNA complexes known as TOPI cleavage complexes (TOPIccs). However, DNA base modifications (oxidation, alkylation, base mismatch, and base loss), carcinogenic

Ethical standards: This research was performed in compliance with the Declaration of Helsinki and with the approval of the ethics board of the Tehran University of Medical Sciences (TUMS; IR.TUMS.SHARIATI.REC.1402.135) in Iran.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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DNA adducts, and other external agents such as camptothecin can stabilize these complexes rendering them irreversible. These stabilized structures, known as abortive TOPIccs, pose a significant threat to DNA integrity. For example, TOPIccs damage the genome by generating DNA double-strand ends upon replication and transcription fork collisions. TOP1 abortive complexes also hinder the transcribing RNA polymerase II during transcription. To mitigate these issues, abortive TOPIccs become ubiquitinated and subsequently degraded by the proteasome system. Partially degraded TOP1 peptide remains covalently bound to the 3′ end of the break. Although TDP1 cannot remove full-length native TOP1, proteolytic digestion or denaturation of TOP1 enables hydrolysis by TDP1; TDP1 removes TOP1 adducts by hydrolyzing the covalent bond between TOP1 catalytic tyrosine and the 3' end of DNA and repairs the abortive TOPIccs. This repair process involves two steps: TDP1 first separates the TOP1 peptide from DNA, creating an intermediate TDP1cc complex, and then resolves itself using its *His493 residue* to finalize the repair. This results in release of TDP1 from DNA. In this way, TDP1 protects the genome from single-strand breaks and prevents double-strand breaks (DSBs).[4-10]

Spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) is an extremely rare autosomal recessive neurodegenerative disease mainly linked to a specific mutation, NM_018319.4: c.1478A>G:p.His493Arg, within the *TDP1* gene, which was initially documented in the year 2002.[1] This mutation involves replacing the highly conserved amino acid His493, located in the catalytic domain, with arginine, disrupting TDP1's active site and likely leading to the SCAN1 phenotype. SCAN1 is primarily characterized by late-onset progressive ataxia, axonal neuropathy, and cerebellar atrophy. Gaze nystagmus may develop after the ataxic gait. Dysarthria and cognitive impairment are less common.[3,11-13] So far, only three families with SCAN1 with p.His493Arg mutation in the *TDP1* gene have been reported worldwide, one from Saudi Arabia and two unrelated families from Oman.[1,11] Very recently, a novel variant in *TDP1*, c.1432C>T:p.His478Tyr, was reported in a Pakistani case.[14] Although they have mentioned this patient as SCAN1, her phenotype is significantly different from the previous three families,[14] and this may be a SCAN1-like disorder or even a novel phenotype.

It appears that the mutations in this particular gene are implicated not only in SCAN1 but also in a range of other pathologic conditions, including cerebellar ataxia,[15] male infertility,[16] and may be pulmonary fibrosis.[17] However, these associations are not definitive due to insufficient information.

Here, we present the fifth family with SCAN1 originating from Iran, as a Middle Eastern country. This family once more exhibited the identical mutation, NM_018319.4: c.1478A>G:p.His493Arg, as previously documented in the literature.[1,11] It seems that this particular mutation may represent a founder mutation within this region; however, the inability to access the haplotype data of these families precludes a thorough examination of this hypothesis. Furthermore, it is imperative to acknowledge that this codon may additionally function as a hotspot codon. We also compare the clinical characteristics of our patients with those of other reported SCAN1 cases with or without common c.1478A>G mutation. Additionally, we conduct a systematic review of all reported *TDP1* gene variants, including those that cause non-neurological conditions, and present the effects of various *TDP1* mutations.

Methods and Materials

Ethical aspects

This study complies with the Helsinki Declaration and received approval from the ethics committee of the Tehran University of Medical Sciences (TUMS: IR.TUMS.SHARIATI.REC.1402.135) in Iran. Written informed consent was obtained from all participants.

Subjects

The proband of this family (III7) (Fig 1A) was referred to the Neuromuscular Research Center of the Shariati Hospital in Tehran, primarily exhibiting axonal neuropathy. After clinical and paraclinical evaluation, the family was subjected to genetic analysis.

Genetic analysis

Whole exome sequencing

Salting out was used to extract DNA from peripheral blood. To do exon capture, the SureSelect V6-Post kit was used. The Illumina HiSeq 4000 System was utilized for the sequencing process. UCSC NCBI37/hg19 is the human reference genome that sequences were aligned to in the whole exome sequencing (WES) study. Burrows-Wheeler Aligner, SAMTools, Picard, and the Genome Analysis Toolkit were among the tools used for variant calling. Variants having a minor allele frequency > 0.01 in population datasets (gnomAD, 1000Genome, ExAC, Esp6500si, and IRANOME) were filtered out, including intronic, intergenic, untranslated regions, synonymous and nonsynonymous exonic variants. The remaining variants were analyzed to determine which ones are found in the genes linked to neuropathy and other neurodegenerative disorders.

Segregation analysis

Primers were designed for the specific candidate variant of *TDP1*: c.1478A>G. The DNA fragment harboring the variant was subjected to amplification through the polymerase chain reaction. Primer sequences are available upon request. Subsequent Sanger sequencing of the polymerase chain reaction product was conducted utilizing the ABI3130 genetic analyzer (Applied Biosystems, Foster City, CA, USA) to validate the presence of the candidate variant.

In silico analysis

The pathogenicity of the candidate variant was predicted using computational tools such as PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (https://sift.bii.a-star.edu.sg/), MutationAssessor (http://mutationassessor.org/r3/), and MutationTaster (https://www.mutationtaster.org/). The variant was classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG).[18]

Systematic review and search method

In accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, we conducted a search for relevant articles across four databases: PubMed, Science Direct, Scopus, and Google Scholar, using the following terms: (1) TDP1, (2) tyrosyl-DNA phosphodiesterase, (3) SCAN1, and (4) spinocerebellar ataxia with axonal neuropathy. We also carried out a manual search to ensure all pertinent articles were considered. During the primary screening, we used EndNote 21 to exclude non-English, duplicate, and completely irrelevant articles. The secondary screening involved reviewing the titles and abstracts of all accessible articles to determine which were eligible for full-text screening. In the full text, or tertiary screening, we excluded any remaining irrelevant articles, resulting in the selection of eligible articles for qualitative synthesis/systematic review (Fig 2).

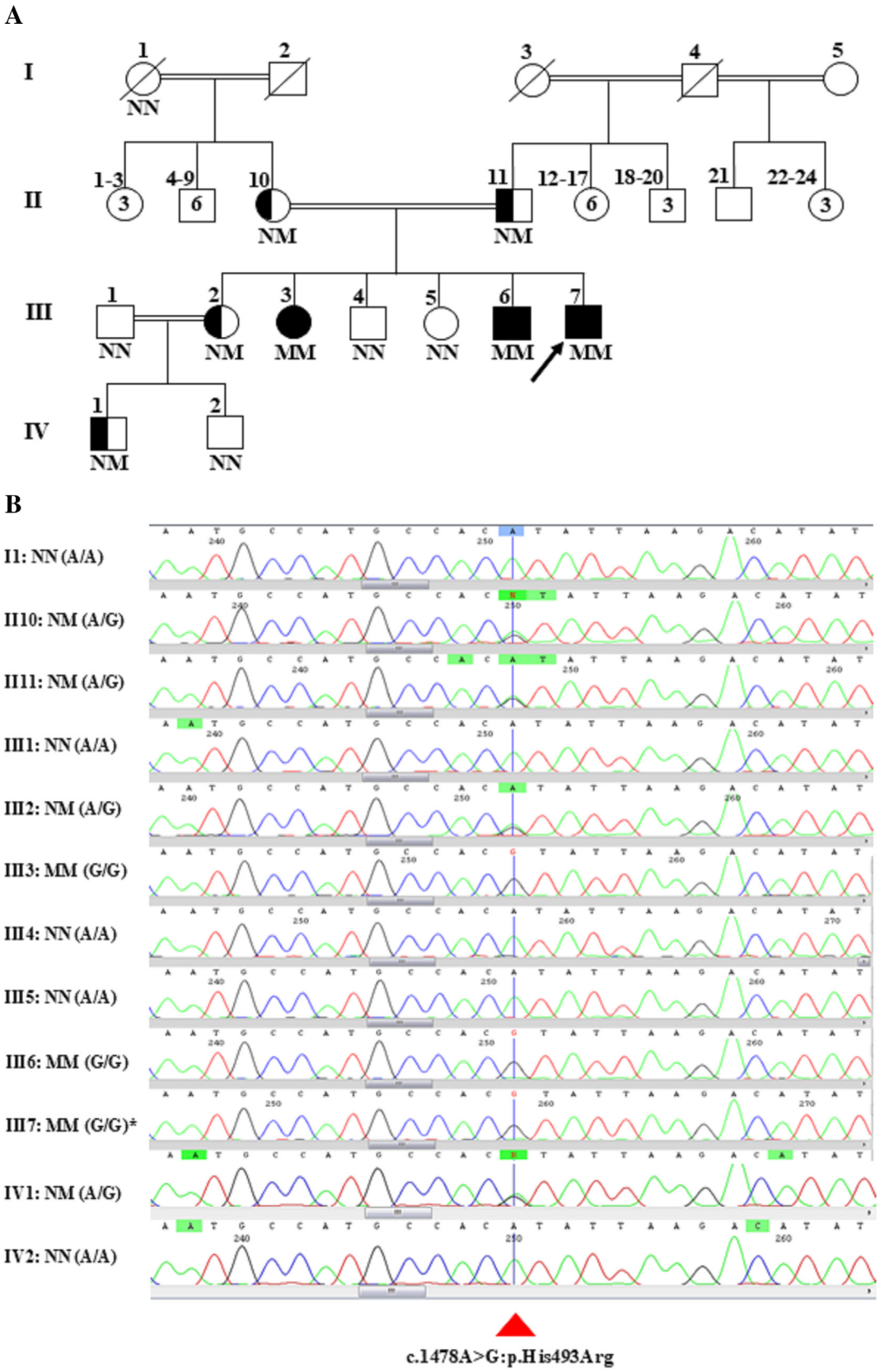

FIGURE 1. (A) Family 1 pedigree with c.1478A>G:p.His493Arg variant in the *TDP1* gene. Genotypes of the *TDP1* variant are shown when individuals were assessed. The arrow denotes the proband. Blank circles, normal females; blank squares, normal males; dark circle, affected female; dark squares, affected males; left filled symbols, heterozygote individuals. (B) Sequence chromatograms of c.1478A>G:p.His493Arg variant in the *TDP1* gene in family 1 members. M, mutant allele; N, normal (wild type) allele; *, proband. The color version of this figure is available in the online edition.

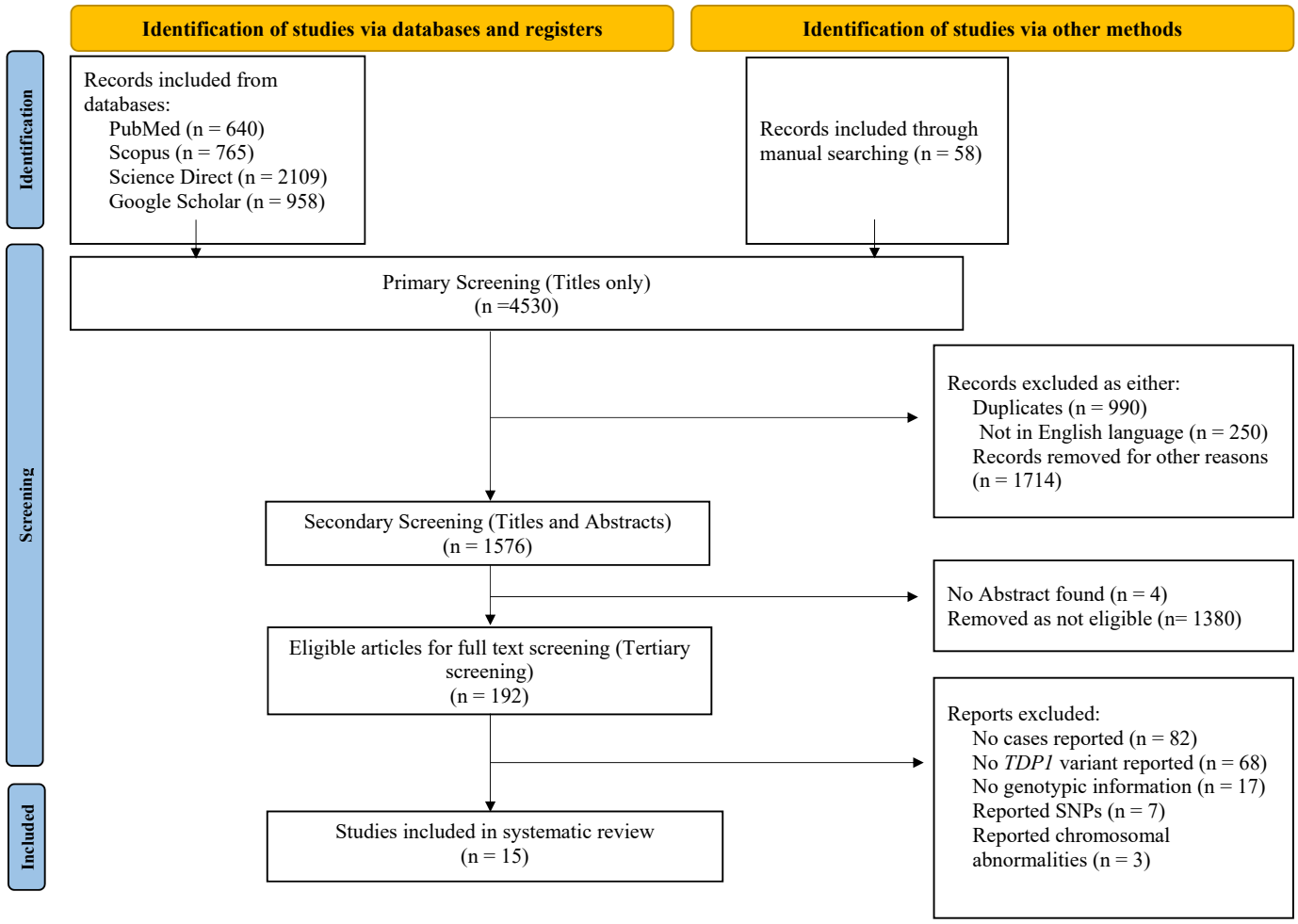

FIGURE 2. PRISMA 2020 flow diagram for this systematic review, which included searches of databases, registers, and other sources. The color version of this figure is available in the online edition.

Analysis of the structural effect of p.His493Arg and p.His478Tyr variants on the TDP1 protein using HOPE web server

HOPE (https://www3.cmbi.umcn.nl/hope/) is an online tool, developed by the Centre for Molecular and Biomolecular Informatics at Radboud University in Nijmegen, which provides information regarding the effects of a particular mutation on the protein structure.[19] The amino acid sequence of TDP1 protein and its variants, p.His493Arg and p.His478Tyr, were introduced to the HOPE database. The probable effects of these variants on the protein structure were predicted.

Results

Subjects

Three affected subjects of family 1 (Fig 1A) were referred to the Neuromuscular Research Center of the Shariati Hospital in Tehran, primarily exhibiting axonal neuropathy. These subjects underwent detailed neurological examination, electrodiagnostic studies, and brain magnetic resonance imaging.

Clinical and paraclinical manifestations

The proband (III7) was a 30-year-old man who presented with slowly progressive distal lower extremity weakness leading to gait difficulty and foot drop, from age 24 years. He also reported progressive ataxia from age 26 years. At age 29 years, he noticed mild hand weakness and difficulty in fine manual motor skills. He also had minor sensory symptoms such as nocturnal paresthesia of his soles. On examination, cognition and speech were normal. Ocular movements including saccades and pursuits were normal, and he did not have nystagmus. Distal limb weakness and atrophy of intrinsic hand and foot muscles were noted (muscle force Medical Research Council score, right/left: first dorsal interossei 3/3, thumb abductors 4/4, finger extensors 4+/4+, gastrocnemius and tibialis anterior muscles 2/2). Strength of proximal and axial muscles was normal. He did not have foot deformity. All deep tendon reflexes were absent, and plantar reflex was downward. Pinprick and light touch sensations were impaired with a stocking-gloves distribution. Vibration and proprioceptive sensations were impaired only in distal lower extremities. He had a wide-based slapping gait and required the assistance of a cane to walk. Finger-to-nose test was normal, but he was unable to tandem walk. Brain magnetic resonance imaging revealed marked symmetric cerebellar atrophy (Fig 3).

In nerve conduction studies, sensory nerve action potentials were unobtainable in all four limbs. Peroneal and tibial compound muscle action potentials were absent, and median and ulnar responses were of low amplitude with normal or slightly reduced conduction velocities (45 to 51 m/s). Electromyography showed neurogenic motor unit action potentials and active denervation with a distal to proximal gradient, more prominent in distal lower

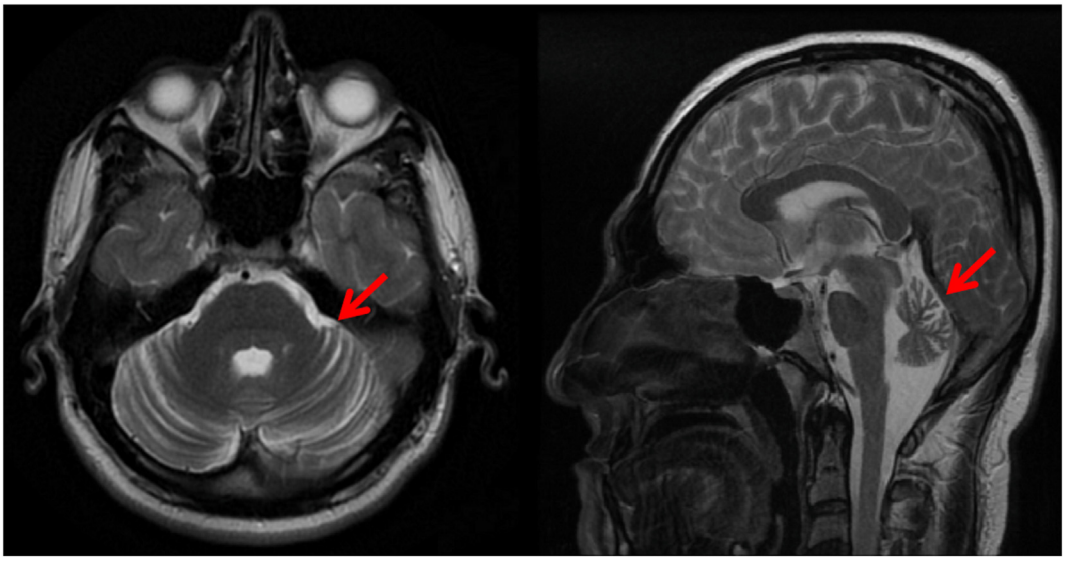

FIGURE 3. Brain magnetic resonance imaging of case III7. The red arrows reveal marked symmetric cerebellar atrophy. The color version of this figure is available in the online edition.

extremities. These features are compatible with chronic axonal sensorimotor polyneuropathy.

He has two older affected siblings, one sister (III3) and one brother (III6), with similar symptoms; both his affected siblings also presented their disease with distal lower limb weakness and walking difficulties. Unlike the proband, they manifested dysarthria. Head titubation and vascular malformation was only observed in cases III6 and III3, respectively. Their detailed clinical manifestations are summarized in Table 1.

Genetic findings

WES data identified a known homozygous variant NM_018319.4: c.1478A>G:p.His493Arg, in the *TDP1* gene in proband (III7). This variant was subsequently verified in the proband through Sanger sequencing. Sanger sequencing also confirmed that his parents (II10 and II11) were heterozygote carriers of the *TDP1* variant and validated the presence of the homozygous variant in both his affected brother (III6) and sister (III3) (Fig 1A). None of the remaining healthy members within the family harbored this variant in the homozygous state.

Systematic review

After initially removing duplicate articles from the same database, we included 640 articles from PubMed, 765 from Scopus, 958 from Google Scholar, and 2109 from Science Direct for primary screening, which involved screening titles only. Additionally, 58 articles were included through manual searches of articles published since 2020 in databases like Springer and ResearchGate. In total, 4530 articles underwent primary screening. From these we excluded non-English articles (250), duplicates (990), and 1714 articles for other reasons (e.g., pre-2000 articles, book chapters). This left 1576 articles for secondary screening, which included title and abstract reviews. Of these, four articles lacked abstracts and 1380 were deemed ineligible for full-text screening, resulting in 1384 exclusions. The remaining 192 articles were eligible for tertiary screening (full-text review). Further exclusions were made for the following reasons: no cases reported (82), cases reported but no *TDP1* mutation (68), case reports without genotype information (17), articles reporting single nucleotide polymorphisms (no disease-causing variants or disease-associated variants) (seven), and articles reporting chromosomal abnormalities of chromosome 14 involving the *TDP1* gene (three) (Fig 2).[20-22]

Ultimately, 15 articles were included in the qualitative synthesis, revealing a total of 16 variants (in 20 families; four with the same variant, p.His493Arg) that may be associated with different phenotypes including neurological and non-neurological diseases (Figs 2 and 4). A summary of reported *TDP1* variants is provided in Table 2. Among these, some families had neurological presentations: (1) three families with SCAN1 that had the same variant as us in homozygous state (rows 1 and 5 of Table 2)[1,11]; (2) a patient with ataxia who carried the same variant but in the heterozygous state; however, its association with the disease was not established (row 6 of Table 2)[25]; and (3) three other families affected with ataxia who harbored three distinct variants in *TDP1*, namely, c.1342C>T, c.560-1G>A, and c.346A>G (rows 15, 12, and 11 of Table 2, respectively). The association of these variants with the disease was challenging. Heterozygous variant c.1342C>T was ruled out because this variant was inconsistent with the disease phenotype, and later a pathogenic variant was identified in the *PRNP* gene by another next-generation sequencing panel in this case.[31] Heterozygous variant c.560-1G>A was a likely pathogenic variant found in three individuals of an American family; the proband of this family presented with poor balance during walking and abnormal eye movements, *but not peripheral neuropathy*. His/her mother had similar gait problems, but she lived until age 94 years. Interestingly, his/her son suffered from a tumor at age nine years and died from another tumor at age 33. The mode of inheritance in this family is probably dominant.[28] Homozygous variant c.346A>G was detected in a sporadic American case. His age at onset (AAO) was in early thirties, and he presented with ataxia and polyneuropathy. No other clinical data were reported for this patient. According to the ACMG criteria, the c.346A>G variant was a variant of uncertain significance that tends to be benign (https://franklin.genoox.com/clinical-db/home) and has not been confirmed in the family (no segregation analysis has been done). Also, there are no strong and functional data to confirm the pathogenicity of the candidate variant.[15] (4) One family with autosomal recessive spastic ataxia of Charlevoix-Saguenay disease harbored a homozygous variant, p.Ser31Cys, in *TDP1*, but the pathogenicity of this variant was ruled out after identification of a homozygous mutation in the

TABLE 1.
All Reported SCAN1 Cases Including This Study Who Carried a *TDP1* Variant

Index	Previous Studies								This Study		
	Takashima et al., 2002[1]			Scott et al., 2019[11]				Ahmad et al., 2024[14]			
Demographic information											
Family ID	SCAN1-1			SCAN1-2	SCAN1-3			SCAN1-4	Family 1		
Patient ID	II1	II2	II3	IV4	VI1	VI3	VI4	IV1	III7	III6	III3
Gender	M	F	M	F	M	M	F	F	M	M	F
Consanguinity	Yes			Yes	Yes			Yes	Yes		
Nationality	Saudi Arabian			Omani	Omani			Pakistani	Iranian		
Age of onset	15	13	13	24	25	24	26	Congenital	24	22	25
Age	56	36	38	NA	NA	NA	NA	NA	30	33	42
Molecular findings											
cDNA change	c.1478A>G			c.1478A>G	c.1478A>G			c.1432C>T	c.1478A>G		
Amino acid change	p.His493Arg			p.His493Arg	p.His493Arg			p.His478Tyr	p.His493Arg		
Known/novel	Novel			Known	Known			Novel	Known		
Protein domain	Catalytical domain			Catalytical domain	Catalytical domain			Catalytical domain	Catalytical domain		
Zygosity	Hom			Hom	Hom			Hom	Hom		
Clinical findings											
Initial symptom	Walking difficulties			Gait ataxia	Gait ataxia and LL weakness			Generalized hypotonia	Walking difficulties and distal LL weakness		
Pes cavus deformity	+	+	+	+	−	−	−	+	−	−	−
Sensory alterations	+	+	+	+	+	+	+	+	+	+	+
DTR	Absent			Absent	Absent			NA	Absent	Absent	Absent
Gait ataxia	+	+	+	+	+	+	+	+	+	+	+
Neuropathy	+	+	+	+	+	+	+	+	+	+	+
Cognitive impairment	−	−	−	+	+	+	+	+	−	−	−
Hand amyotrophy	+	+	+	+	+	+	+	NA	+	+	+
Gaze-evoked nystagmus	+	+	+	+	+	+	+	NA	−	−	−
Distal upper limb weakness	+	+	+	+	+	+	+	NA	+	+	+
Dysarthria	+	+	+	+	+	−	−	+	−	+	+
SARA score	NA	NA	NA	13.5	14.5	14	9	NA	11	20	21
Others	Seizure, cholelithiasis	NA	Cholelithiasis	Dyskinesia, bradykinesia, sphincter dysfunction, double vision, ptosis, or dysphagia	Poorly controlled diabetes mellitus	NA	Poorly controlled diabetes mellitus	Kyphoscoliosis, seizure, hearing loss, visual impairment	NA	Head titubation, cervical dystonia, and truncal ataxia	Truncal ataxia, “retropharyngeal” vascular malformation
Electrodiagnostics											
Median motor NCV (m/s)	44	53.1	62.7	Normal	NA			NA	45.1	41.4	47.2
Median sensory NCV (m/s)	Absent	Absent	Absent	Absent	Absent			NA	NA	NA	30.8
Median motor amplitude (mV)	NA	NA	NA	Reduced	NA			NA	3.4	0.3	0.5
Median distal latency (ms)	NA	NA	NA	Normal	NA			NA	4.35	4.9	4.55

Biochemical findings										
Serum cholesterol level	Elevated		Elevated	Elevated		NA	NA	NA	Elevated	
Serum albumin level	Low		Low	Low		NA	NA		Low	
Serum AFP level	NA		Normal	Elevated		NA				
MRI										
Brain & spinal cord MRI	Cerebellar vermis atrophy	Cerebellar atrophy, mild cerebral atrophy	Cerebellar atrophy, mild frontotemporal lobe atrophy	Cerebellar atrophy	Cerebellar atrophy	NA	Cerebellar atrophy			

Abbreviations:
AFP = Alpha fetoprotein
cDNA = Complementary DNA
DTR = Deep tendon reflexes
F = Female
Hom = Homozygous
LL = Lower limb
M = Male
MRI = Magnetic resonance imaging
NA = Not available
NCV = Nerve conduction velocity
SARA = Scale for Assessment and Rating of Ataxia
SCAN1 = Spinocerebellar ataxia with axonal neuropathy type 1

SACS gene (row 13 of Table 2).[29] (5) The c.1697C>T variant has been documented in two different studies (rows 2 and 7 of Table 2). (i) In screening of 187 Japanese individuals affected by autosomal recessive or sporadic spinocerebellar ataxias, this variant was found in heterozygous state, but no second variant was found. Therefore, this variant was not considered as disease causing (row 2 of Table 2).[1] (ii) In a 34-year-old Korean female with ataxia, extrapyramidal sign, and oculomotor abnormalities, this variant was found in homozygous state, but no segregation data are available and the result was inconclusive (row 7 of Table 2).[26] (6) Very recently and during the review of our manuscript, a new female originating from Pakistan has been described who presented an apparently SCAN1-like phenotype. WES result of the proband revealed a novel homozygous variant, c.1432C>T, in the *TDP1* gene (row 19 of Table 2).[14] This variant is the second mutation in this gene associated with the SCAN1 or a SCAN1-like phenotype.

The structural effect of p.His493Arg and p.His478Tyr variants on the TDP1 protein using HOPE

The results indicated that the p.His493Arg variant changes the properties of the active site and eventually disrupts the protein function. However, for the p.His478Tyr variant, histidine—a charged amino acid—is replaced by an uncharged tyrosine, and this change would possibly change the protein conformation and ultimately interrupts the bond formation of the protein (Supplementary Figure S1).

Discussion

Based on our systematic review, *TDP1* variants may be associated with different phenotypes that are provided in Table 2, including some types of cancers (rows 4 and 8),[27] infertility (rows 9 and 10),[16] pulmonary fibrosis (rows 16 to 18),[17] ataxia (rows 2, 6, 7, 11, 12, and 15),[15] autism spectrum disorder (row 3),[23] and specifically SCAN1 (rows 1, 5, and 19).[1,11,14] Until recently, the homozygous variant c.1478A>G in *TDP1* was the only variant with an established role in SCAN1 phenotype. In late 2024, a novel homozygous variant in *TDP1* was reported in a Pakistani case afflicted to SCAN1 or may be a SCAN1-like phenotype.[14]

SCAN1 is an ultrarare autosomal recessive condition, and previous studies have identified this disease in only four families: one from Saudi Arabia and two seemingly unrelated consanguineous families from Oman who carried c.1478A>G variant in the *TDP1* gene and a recently reported Pakistani family with a distinct novel variant, c.1432C>T, in *TDP1*.[1,11,14] This study reports the fifth SCAN1 family overall and the first Iranian family with c.1478A>G variant in *TDP1*. Given the geographic proximity of Saudi Arabia, Oman, and Iran, we suggest that the *TDP1*:c.1478A>G variant may be a founder mutation among families with a Middle Eastern background. In confirmation of this point, it has been determined that the probands of two Omani families shared the same haplotype,[11] indicating that the Saudi Arabian family and our Iranian subjects might also share this haplotype. Further analysis is needed to confirm this hypothesis.

According to our systematic review, although typical symptoms of SCAN1, ataxia, and polyneuropathy were observed in all patients (totally 11 cases), they presented some phenotypic heterogeneities (AAO and clinical features). The mean AAO of the disease in these cases was 19.18 ± 7.7; however, the AAO of the disease in the Pakistani patient was much lower than the average; she had the lowest AAO at birth.[14] The AAO of disease in our patients was more similar to that of Omani patients, and they experienced disease onset later, in their third decade of life (range 22 to 26).[11] Despite the same AAO in our patients and Omani patients, clinical

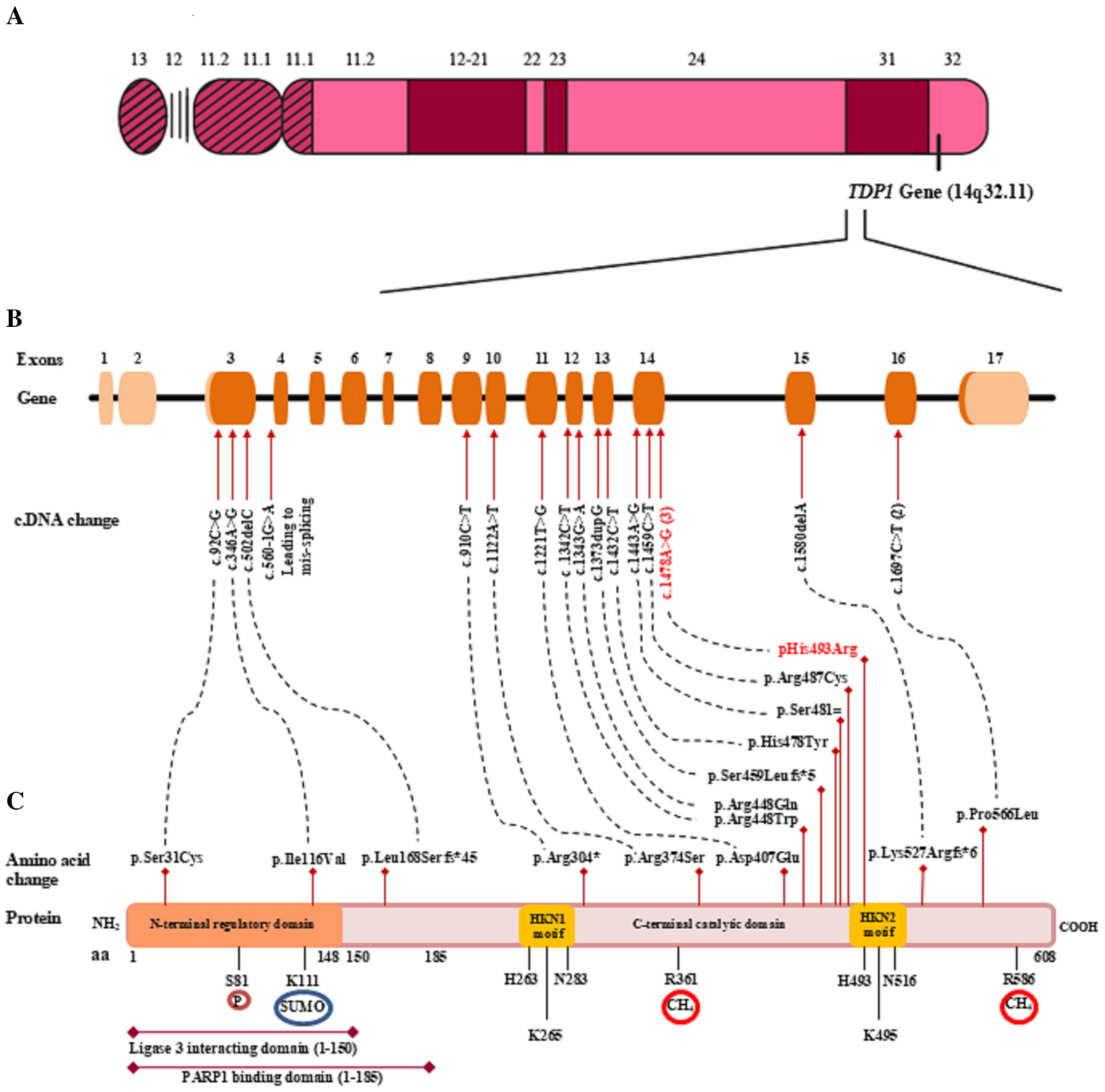

FIGURE 4. The human *TDP1* gene and protein. Location of *TDP1* on chromosome 14 (A). Structure and reported variants in the *TDP1* gene (B) and protein (C). Each variant in the cDNA level is connected to its correspondence in the protein level by a dotted line. Our variant was shown in red. 3: This variant has been identified three times (four families) in patients with SCAN1 including this study. 2: This variant has been reported two times in different articles. Light orange, noncoding exons; dark orange, coding exons; P, phosphorylation site; SUMO, SUMOylation site; CH_4, methylation site. The color version of this figure is available in the online edition.

heterogeneity was evident; our patients like the Saudi Arabian patients and unlike Omani and Pakistani cases did not have cognitive impairment. In total, pes cavus deformity, cognitive impairment, nystagmus, and dysarthria were observed in five of 11 (~45.5%), five of 11 (~45.5%), seven of 11 (~63.6%), and eight of 11 (~72.7%) cases, respectively (Table 1).

It is interesting that clinical heterogeneity was evident not only in different families with distinct variants but also in families with the same variant as well as in the patients of the same family. For instance, dysarthria was only detected in subject VI1 in SCAN1-3 Omani family (Table 1). Such heterogeneities are not specific to SCAN1 and have been observed in other neurodegenerative diseases.[32] These heterogeneities may be due to the involvement of other genetic, epigenetic, and environmental factors.

On the other hand, it should be noted that as a result of advancements in next-generation sequencing methodologies, the c.1478A>G variant and consequently SCAN1 disease may not be restricted to the Middle East and along with additional variants such as c.1432C>T within this gene,[14] has the potential to be documented in various global regions in the future. Before 2024,

TABLE 2.
Reported Variants of *TDP1* During Our Systematic Review Until December 2024

Number of Variants	cDNA C hange	Amino Acid Change	Mutation Type	Zygosity	Phenotype	ACMG Classification	Ref.	Comment
1†	**c.1478A>G**†	**p.His493Arg**†	**Missense**†	**Hom**†	**SCAN1**†	**P (PM3, PS3, PP3, PM2)**†	1†	First report of our variant†
2‡	c.1697C>T‡	p.Pro566Leu‡	Missense‡	Het‡	Ataxia‡	LB (PM2, BP4, BP6)‡	1‡	No second variant was found‡
3	c.1122A>T	p.Arg374Ser	Missense	NA	ASD	VUS (PM2)	23	-
4	c.502delC	p.Leu168Serfs*45	Frameshift Deletion	NA	Breast cancer	LP (PVS1, PM2)	24	-
5†	c.1478A>G*,†	p.His493Arg†	Missense†	Hom†	SCAN1†	P (PM3, PS3, PP3, PM2)†	11†	The mutation was previously reported by Takashima et al., 2002†
6†	c.1478A>G†	p.His493Arg†	Missense†	Het†	Ataxia†	P (PM3, PS3, PP3, PM2)†	25†	This variant was not the cause of the disease in this patient†
7‡	c.1697C>T‡	p.Pro566Leu‡	Missense‡	Hom‡	Ataxia‡	LB (PM2, BP4, BP6)‡	26‡	Inconclusive results‡
8	c.1343G>A	p.Arg448Gln	Missense	Het	Low-grade g lioma	VUS (BS2)	27	-
9	c.1459C>T	p.Arg487Cys	Missense	Hom	Male infertility	VUS (PM2, PP3)	16	No evidence of neurological involvement
10	c.910C>T	p.Arg304*	Splicing	Hom	Male infertility	P (PM3, PVS1, PM2)	16	No evidence of neurological involvement
11	c.346A>G	p.Ile116Val	Missense	Hom	Ataxia	VUS (PM2, BP4)	15	Inconclusive results
12	c.560-1G>A	Mis-splicing	Splicing	Het	Ataxia	LP (PVS1, PM2)	28	-
13	c.92C>G	p.Ser31Cys	Missense	Hom	ARSACS	VUS (PM2)	29	Disease-causing variant was found in the *SACS* gene and *TDP1* variant ruled out
14	c.1221T>G	p.Asp407Glu	Missense	Het	Heart defect	VUS (PM2)	30	The variant was not considered as disease-causing variant
15	c.1342C>T	p.Arg448Trp	Missense	Het	Ataxia	VUS (PM2, BS2)	31	Disease-causing variant later found in *PRNP* gene and *TDP1* variant ruled out
16	c.1373dupG	p.Ser459Leufs*5	Frameshift Duplication	Het	Pulmonary fibrosis	LP (PVS1, PM2)	17	Considered as likely disease-causing variant
17	c.1580delA	p.Lys527Argfs*6	Frameshift Deletion	Het	Pulmonary fibrosis	LP (PVS1, PM2)	17	No material available for segregation analysis
18	c.1443A>G	p.Ser481=	Synonymous	Het	Pulmonary fibrosis	VUS (PM2, BP7)	17	Lack of segregation in the family
19	c.1432C>T	p.His478Tyr	Missense	Hom	SCAN1	VUS (PM2, PP3)	14	-

Abbreviations:
ACMG = American College of Medical Genetics and Genomics
ARSACS = Autosomal recessive spastic ataxia of Charlevoix-Saguenay
ASD = Autism spectrum disorder
cDNA = Complementary DNA
Het = Heterozygous
Hom = Homozygous
LB = Likely benign (data are taken from the Franklin database: https://franklin.genoox.com/clinical-db/home)
LP = Likely pathogenic
NA = Not available
P = Pathogenic
Ref. = Reference
SCAN1 = Spinocerebellar ataxia with axonal neuropathy 1
VUS = Variant of unknown significance
Our variant has been shown in bold. Identical variants have been shown in † and ‡.
Data for LB, LP, VUS, and P are taken from the Franklin database: https://franklin.genoox.com/clinical-db/home.
* Two families have been reported by Scott et al.

the only mutation reported in the patients with SCAN1 was c.1478A>G. In late 2024, a novel variant of c.1432C>T was reported in a Pakistani case. This case presented with generalized hypotonia at birth. She had severe kyphoscoliosis and cognitive, hearing, and visual impairments. She also manifested with seizures at age nine months. Although the clinical manifestations of this case were somewhat different than typical SCAN1 phenotype, we propose two hypotheses for this variant: (1) the clinical spectrum of this disease is broader than what has been reported so far and this novel variant may be linked to a more severe form of SCAN1 and (2) this particular variant may contribute to a novel distinct neurological disorder, which is not impossible due to the critical roles of TDP1 protein in DNA repair pathways.[14] More cases and investigation are needed to confirm any of these hypotheses. In this regard, our systematic review also specified that mutations in this gene may be associated with other neurological or non-neurological diseases, in addition to SCAN1 disease. Ngo et al. in 2020, during genetic analysis of a large cohort of predominantly adult and sporadic patients affected with ataxias (260 cases) identified a novel homozygous variant in *TDP1*, c.346A>G:p.Ile116Val, in a 56-year-old American male exhibiting adult-onset ataxia.[15] The details of his clinical features are not available, and the authors have only mentioned ataxia and polyneuropathy in supplementary table 4 of their article. Furthermore, there is a lack of segregation data and additional functional studies to confirm the pathogenic nature of this variant.[15] The variant is classified as variant of uncertain significance that tends to be benign in Franklin database, and its role in disease causation remains ambiguous.

Should this variant indeed be implicated as the etiologic factor for the disease, it would represent the second documented instance

of a homozygous variant, distinct from the c.1478A>G variant, in the *TDP1* gene among patients with SCAN1 and the first case without a Middle Eastern ancestry.

Another interesting variant that occurred in the *TDP1* gene and was associated with cerebellar ataxia and was reported again in an American family is a heterozygous splice site variant, c.560-1G>A.[28] Based on ACMG criteria this variant is a likely pathogenic variant and may disrupt normal splicing of *TDP1* mRNA. As mentioned in the "Results" section, the proband of this family presented with a poor balance during walking and abnormal eye movements, although peripheral neuropathy was absent. His/her mother displayed similar gait abnormalities; she reached age 94 years. Notably, his/her son experienced a neoplasm at age nine years and subsequently died from another neoplasm at age 33 years. All of them carried the heterozygous variant of c.560-1G>A, and the second variant in *TDP1* was not detected. So the pattern of inheritance in this family was considered as autosomal dominant.[28] Although the association between this specific mutation and cancer in this case remains indeterminate, due to the role of this gene in the repair of DNA DSBs such an association can be considered. It should also be noted that the association between *TDP1* variants and some types of cancer has been reported previously.[27] Jane et al. also demonstrated that B lymphoblastoid cell lines derived from these cases exhibit a 70% reduction in baseline expression of TDP1 when compared with normal cell lines, as determined through western blot analysis; they considered that the c.560-1G>A variant is the pathogenic variant in this family. This particular variant represents the sole mutation that has been linked to ataxia in the heterozygous state. It should be noted that the data presented in this report have not been disseminated as an official publication in a valid academic journal, and it appears that the findings of an undergraduate thesis have been made publicly available.[28]

As mentioned earlier, *TDP*1 gene mutations, in addition to SCAN1 and ataxia, have also been reported in several other diseases such as autism spectrum disorder, breast cancer,[24] glioma, male infertility, solid tumors, heart defects,[30] and pulmonary fibrosis (Table 2). Although the role of TDP1 in these conditions is not conclusive, its critical function in DNA repair and broad expression suggests that *TDP1* variants could plausibly cause these diverse phenotypes.

TDP1 is the main enzyme responsible for repairing DNA damage caused by topoisomerase I that can prevent transcription. Two specific histidine amino acids (His263 and His493) in TDP1's structure work together to remove the broken part of the DNA. First, His263 attacks the broken part, releasing a piece of the DNA and forming a temporary bond with the DNA. Then, His493 helps to break this bond with the help of a water molecule. After TDP1 is released, other enzymes (PNKP [polynucleotide kinase phosphatase] and LIG3 [DNA ligase 3]) fix the remaining damage and complete the DNA repair.[10,33]

Cells derived from patients with SCAN1 carrying the p.His493Arg variant exhibited a 100-fold decrease in TDP1 protein activity, which was the result of both decreased enzymatic function and protein levels of mutant TDP1.[34,35] Previous studies proposed that homozygous variants causing SCAN1 phenotype act through a loss-of-function mechanism. However, more recent studies support a gain-of-function mechanism, as the accumulation of abortive TOP1ccs and TDP1ccs occurs due to the absence of functional protein to resolve these complexes, ultimately causing DSBs. This gain-of-function hypothesis is further strengthened by observations of mild or absent neurodegeneration in *TDP1*-deficient animal models.[36] On the other hand, although heterozygous variants cause a reduction in TDP1 protein, these variants do not result in the SCAN1 phenotype. Instead, they appear to be related with a milder ataxic phenotype and an increased predisposition to tumorigenesis; this may be due to the fact that functional protein is still present and resolves the abortive complexes. The occurrence of ataxic features and tumorigenesis might be related to failure of TDP1 protein in a different unknown but crucial function.[28]

The results of HOPE database on protein modeling showed that the p.His493Arg variant disrupts the active site, causes loss of interaction with an important ligand, and eventually disables the protein function (Supplementary Figure S1). When TDP1 is deficient or mutated, DNA breaks take longer to repair. The TDP1 p.His493Arg variant completely prevents repair; this is because the mutant protein sticks to DNA, leading to DNA damage and cell death. Therefore the p.His493Arg variant in the catalytic domain of TDP1 disrupts its ability to resolve TOPI-induced DNA damage, and it may lead to dysfunction of neurons and their destruction, which ultimately leads to SCAN1-related features.[34,36-38] For the p.His478Tyr variant, it suggested that the mutant form will cause a change in hydrophobicity and may disrupt the hydrogen bond formation. These results are in accordance with the previous studies by Takashima et al. and Ahmad et al.[1,14]

TDP1's function has also been studied in various models such as zebrafish,[39] mice,[40] flies,[41] yeast,[42,43] and human cells.[36] In zebrafish they observed that TDP1 in zebrafish embryos does not appear to be crucial for repairing topoisomerase I-induced DNA damage, as evidenced by the lack of increased sensitivity to topoisomerase I inhibitors at this developmental stage.[39] In human cell experiment they found that cells with SCAN1 have higher levels of topoisomerase I-induced DNA damage, changes in gene expression, and abnormal DNA structures called R-loops. These changes lead to more DNA breaks that are harder to repair. It has been also discovered that another protein called TDP2 can help repair DNA breaks in cells without TDP1, but not in cells with the mutant form of TDP1 (p.His493Arg).[36]

Although there have been many studies in this area, the exact molecular process that causes the SCAN1 phenotype is still unknown. Our study offers a comprehensive overview of reported *TDP1* variants, and their associated phenotypes, which can contribute to our understanding of its disease-causing mechanisms.

Conclusion

Since there have only been four reported families with SCAN1 disease, its phenotypic spectrum has not been fully uncovered. To fully understand SCAN1 disease, more families need to be studied. In this regard, our study led to the identification of a fifth family and expanded the phenotypic spectrum of SCAN1. Among these five Middle Eastern SCAN1 families, only the Pakistani case had a novel variant other than c.1478A>G. Interestingly, four other families including our family carried a possible founder mutation in *TDP1*, c.1478A>G:p.His493Arg. Therefore, it is suggested that for patients from this region who present symptoms of cerebellar ataxia and polyneuropathy before age 30 years (with or without cognitive decline), *TDP1* variants and SCAN1 disease should be prioritized.

Limitations

Patient's performance in the examination of fast altering movements may be influenced by distal weakness, lowering the accuracy of Scale for Assessment and Rating of Ataxia calculation in these patients.

CRediT authorship contribution statement

Mahsa Mohammadi: Writing – original draft, Visualization, Software, Methodology, Investigation. **Moez Ravanbod:** Writing –

original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis. **Aida Ghasemi:** Writing – review & editing, Visualization, Software, Resources, Methodology, Investigation, Formal analysis. **Hadi Gharebaghian:** Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Conceptualization. **Shahriar Nafissi:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Afagh Alavi:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

All authors have reviewed the contents of the manuscript with title "Genetic homogeneity of a *TDP1* variant, c.1478A>G, as the main disease-causing variant of spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) in the Middle East: a systematic review" being submitted and have approved its contents and validated the accuracy of the data.

The data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere, and will not be submitted elsewhere while under consideration at the "Pediatric Neurology."

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pediatrneurol.2024.12.011.

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