

Expanding The Genetic Spectrum of ALS: A Case Series of Rare Variants

Dr. Kalpana P¹, Dr. Alex J², Dr Anisha Ashra³, Dr. Sethuram⁴

¹MBBS, MD, DM(Neurology), Kanyakumari Government Medical college, Kanyakumari, Tamilnadu, India

²MBBS, MD, DM(Neurology), Kanyakumari Government Medical college, Kanyakumari, Tamilnadu, India, email: dralexjebagnanam@gmail.com

³MBBS, MD, DM(Neurology), Kanyakumari Government Medical college, Kanyakumari, Tamilnadu, India

⁴MBBS, Dch, MD, DM(Neurology), Kanyakumari Government Medical college, Kanyakumari, Tamilnadu, India
Corresponding author - Dr Alex J, dralexjebagnanam@gmail.com

Abstract

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by motor neuron loss. While most cases are sporadic, a subset is linked to genetic mutations. Rare genetic variants remain underexplored, yet they may provide important insights into disease mechanisms and clinical heterogeneity. This case series expands the spectrum of genetic associations in ALS and emphasizes the importance of comprehensive genetic testing. Recognition of rare variants may refine diagnostic accuracy, inform prognosis, and guide future therapeutic strategies.

Keywords: Genetic Amyotrophic Lateral Sclerosis (ALS), Motor Neuron Disease, ALS Genetics.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder characterized by degeneration of upper and lower motor neurons in the brain and spinal cord [1]. The disease was first clinically described in the 19th century by Jean-Martin Charcot, who recognized its distinct motor neuron pathology. ALS affects approximately 2 to 3 individuals per 100,000 annually worldwide, with incidence varying slightly across regions [2]. The mean age of onset is around 55 to 65 years, although both younger and older patients have been reported. About 90% of ALS cases are sporadic, while 5–10% are familial, often linked to genetic mutations [3].

Clinically, ALS presents with progressive muscle weakness, fasciculations, spasticity, and eventual paralysis. Bulbar involvement leads to dysarthria and dysphagia, while respiratory muscle weakness contributes to respiratory failure, the most common cause of death. The disease course is typically rapid, with median survival ranging from 3 to 5 years after symptom onset, though variability exists depending on genetic background and phenotype [4].

Genetic factors play a crucial role in ALS pathogenesis. Since the discovery of SOD1 mutations in 1993, more than 40 genes have been implicated, including C9orf72, TARDBP, and FUS. Rare genetic variants continue to be identified, expanding the spectrum of ALS and contributing to its clinical heterogeneity [2]. Recognition of these uncommon correlations is essential for improving diagnostic accuracy, understanding disease mechanisms, and guiding future therapeutic strategies.

2. Aim and Objectives

Aim: To describe the clinico-genetic spectrum of three cases of amyotrophic lateral sclerosis (ALS) with rare genetic correlations.

Objectives:

1. To highlight the clinical presentation and progression patterns in ALS patients with uncommon genetic variants.
2. To analyze radiological and neurophysiological findings in relation to genetic background.
3. To expand understanding of genotype-phenotype correlations in ALS.
4. To emphasize the importance of considering rare genetic mutations in the diagnostic evaluation of ALS.

3. Review of Literature

Amyotrophic lateral sclerosis (ALS) is a progressive, invariably fatal neurodegenerative disorder characterized by degeneration of upper and lower motor neurons in the brain and spinal cord [5]. ALS is clinically classified into sporadic and familial forms. Sporadic ALS (sALS) accounts for approximately 90–95% of cases, while familial ALS (fALS) represents 5–10% and is associated with identifiable genetic mutations [6]. The mean age of onset is between 55 and 65 years, though cases have been reported in both younger and older individuals [7].

Clinically, ALS presents with progressive muscle weakness, fasciculations, spasticity, and bulbar symptoms such as dysarthria and dysphagia. The disease course typically leads to respiratory failure, with median survival ranging from 3 to 5 years after symptom onset [8]. However, variability in progression is influenced by genetic background and phenotype.

Genetic studies have identified more than 40 genes implicated in ALS pathogenesis. The most common mutations include C9orf72, SOD1, TARDBP, and FUS, but rare variants continue to be discovered, expanding the genetic spectrum of ALS [6]. These rare mutations may present with atypical clinical features, slower progression, or overlapping syndromes, underscoring the heterogeneity of the disease [9].

Diagnostic evaluation of ALS relies on clinical criteria supported by neurophysiological studies such as electromyography (EMG). Genetic testing has become increasingly important, not only for identifying familial cases but also for uncovering rare variants in sporadic patients. Advances in next-generation sequencing (NGS) and whole-exome sequencing (WES) have improved detection of uncommon mutations, offering new insights into disease mechanisms and potential therapeutic targets [10].

4. Material and Methods

CASE 1

A 28-year-old male with a past history of jaundice, presented with a chronic progressive neurological illness of 8 years duration. The illness began with weakness of all four limbs, associated with clumsiness and difficulty in performing fine motor tasks. Over time, he developed twisting posturing of both upper limbs and lower limbs, accompanied by stiffness and involuntary brief jerky movements. In the past 6 months, he reported slurring of speech and reduced fluency, with difficulty in articulation. Family history of similar illness present. On examination, the patient was conscious, though inattentive. Speech was dysarthric and effortful. Neurological evaluation revealed axial and appendicular rigidity, fasciculations in thigh muscles, and dystonic posturing of both feet. Muscle power was reduced to 3/5 in upper limbs and 4/5 in lower limbs. Deep tendon reflexes were exaggerated, with bilateral extensor plantar responses. Myoclonus was observed in the tongue, face, and both upper and lower limbs. Primitive reflexes including palmomental and pout reflexes were present, and the glabellar tap was non-accommodative. Based on the clinical profile, the patient was provisionally diagnosed as Familial ALS Plus syndrome, with features of motor neuron disease accompanied by dystonia and myoclonus, consistent with an ALS-Plus phenotype.

CASE 2

A 49-year-old male with no prior comorbidities presented with chronic progressive neurological illness of 3 years duration, initially with weakness of upper limbs in the form of difficulty lifting and holding objects, later involving lower limbs with difficulty rising from squatting and holding footwear. Over the past year, he developed slurring of speech with progressive dysarthria, emotional lability, and dysphagia for solids. Attenders noted involuntary twitching movements and muscle thinning. On examination, patient was conscious and oriented. Wasting and fasciculations were noted in limb and tongue muscles, with spastic dysarthria, frontal dystonia, and neurogenic tremor. Tone was increased with axial and appendicular rigidity. Power was reduced (4/5), reflexes were brisk with bilateral extensor plantar responses. Primitive reflexes (pout, snout, palmomental, Myerson) were present. Clinical diagnosis of ALS Plus syndrome, with motor neuron disease features accompanied by extrapyramidal signs such as dystonia.

CASE 3

A 65-year-old male with no prior comorbidities, presented with low backache, progressive weakness of all four limbs, numbness, and memory disturbances. Symptoms gradually worsened, with functional decline and cognitive impairment noted by family members.

On examination, patient had generalized weakness, spasticity, and exaggerated deep tendon reflexes. Bilateral extensor plantar responses were present. Cognitive testing revealed impaired memory and executive dysfunction. Features of parkinsonism including rigidity and bradykinesia were observed.

5. Results (Including Observations)

Case 1

Routine baseline blood investigations were normal. Viral markers negative. Metabolic parameters were normal. Parathyroid hormone levels were normal. Ultrasound Abdomen and CT chest were normal. NCS Motor

conduction: Reduced compound muscle action potential (CMAP) amplitudes in median, ulnar, tibial, fibular nerves; normal conduction velocities and Sensory conduction: Normal sensory nerve action potentials (SNAPs). EMG: Active denervation with fibrillations and positive sharp waves in left deltoid and right vastus lateralis muscles, Chronic reinnervation changes with large amplitude, long-duration motor unit potentials (MUPs), Fasciculation potentials noted in left deltoid and right vastus lateralis muscles. MRI Brain revealed frontotemporal degeneration and cervical spinal cord with whole spine screening is normal. Genetic testing revealed pathogenic PNPLA6 mutation.

Case 2

Routine baseline blood investigations were normal. Viral markers negative. Metabolic parameters were normal. Parathyroid hormone levels were normal. Ultrasound Abdomen and CT chest were normal. NCS Motor conduction: Reduced compound muscle action potential (CMAP) amplitudes in median, ulnar, tibial, fibular nerves; normal conduction velocities and Sensory conduction: Normal sensory nerve action potentials (SNAPs). EMG: Active denervation with fibrillations and positive sharp waves in right deltoid and left vastus lateralis muscles, Chronic reinnervation changes with large amplitude, long-duration motor unit potentials (MUPs), Fasciculation potentials noted in right deltoid and left vastus lateralis muscles. MRI Brain and cervical spinal cord with whole spine screening is normal. Genetic testing shows ABCA7 mutation.

Case 3

Routine baseline blood investigations were normal. Viral markers negative. Metabolic parameters were normal. Parathyroid hormone levels were normal. Ultrasound Abdomen and CT chest were normal. NCS Motor conduction: Reduced compound muscle action potential (CMAP) amplitudes in median, ulnar, tibial, fibular nerves; normal conduction velocities and Sensory conduction: Normal sensory nerve action potentials (SNAPs). EMG: Active denervation with fibrillations and positive sharp waves in left deltoid and right vastus lateralis muscles, Chronic reinnervation changes with large amplitude, long-duration motor unit potentials (MUPs), Fasciculation potentials noted in left deltoid and right vastus lateralis muscles. MRI Brain revealed frontotemporal degeneration and cervical spinal cord with whole spine screening is normal. Genetic testing revealed pathogenic SAMD9L mutation.

All three patients presented with progressive neurological illness characterized by limb weakness, dystonia, rigidity, and rapid deterioration. Akinetic mutism was noted Case 3. Case 1 had a long disease course with dystonia and jerky movements, consistent with a familial ALS-Plus phenotype. Case 2 showed bulbar and extrapyramidal involvement with emotional lability and dysphagia.

Neurophysiological studies in all cases revealed motor axonal involvement with active denervation and fasciculations, while sensory conduction remained normal. MRI brain consistently demonstrated frontotemporal degeneration. Genetic testing revealed PNPLA6 mutation in Case 1, ABCA7 mutation in Case 2, and SAMD9L mutation in Case 3.

Other causes of rapidly progressive dementia and motor neuron disease were excluded. Based on clinical, radiological, and genetic correlation, all cases were diagnosed as ALS Plus syndromes, with overlapping phenotypes: Familial ALS-Plus (Case 1), ALS-Plus with extrapyramidal signs (Case 2), and ALS-Parkinson's FTD-Dementia complex (Case 3). All patients were treated with supportive measures including syndopa, sodium valproate, and symptomatic therapy, but no significant improvement was observed.

Genetic Associations with ALS

CASE 1: PNPLA6 mutation

Function: Encodes neuropathy target esterase, crucial for neuronal maintenance and lipid metabolism.

Evidence: A 2022 study in *Frontiers in Neurology* described biallelic PNPLA6 variants causing complex neurodegenerative phenotypes including spastic paraplegia, ataxia, and motor neuron disease [11].

ALS correlation: PNPLA6 mutations can manifest with motor neuron degeneration and dystonia, supporting its role in familial ALS-Plus syndromes.

CASE 2: ABCA7 mutation

Function: ATP-binding cassette transporter involved in lipid metabolism and amyloid clearance.

Evidence: Meta-analyses and mechanistic studies show ABCA7 variants increase Alzheimer's and FTD risk by altering lipid transport and amyloid processing [12].

ALS correlation: While not a primary ALS gene, ABCA7 mutations contribute to ALS-Plus with dementia overlap, especially when extrapyramidal and bulbar features are present.

CASE 3: SAMD9L mutation

Function: Encodes sterile alpha motif domain-containing protein 9-like, regulating cell proliferation and antiviral response.

Evidence: A 2025 Blood review highlighted SAMD9L mutations as causative for ataxia-pancytopenia and multisystem neurodegenerative syndromes [13].

ALS correlation: (SAMD9L mutation): This mutation in our case ALS-Parkinson's-Dementia complex is novel, because SAMD9L has not been reported in ALS cohorts. A co-existing neurodegenerative syndrome overlapping ALS, or a potential new association that has not yet been validated in published ALS genetics.

6. Discussion

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by degeneration of upper and lower motor neurons, leading to weakness, spasticity, fasciculations, dysarthria, dysphagia, and respiratory failure [14]. ALS includes classical forms and "ALS Plus" phenotypes, where additional systems are involved such as frontotemporal dysfunction, parkinsonism, dystonia, and bulbar or extrapyramidal signs [15]. While most ALS is sporadic, a subset is hereditary with identifiable gene mutations. Sporadic ALS is the most common form, and its exact triggers are unknown. Proposed mechanisms include excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, RNA processing defects, and neuroinflammation [16]. Familial or hereditary ALS accounts for a minority of cases and is due to pathogenic variants in classical genes such as C9orf72, SOD1, TARDBP, and FUS. Phenotypes range from pure motor neuron disease to ALS Plus, with cognitive, behavioral, and extrapyramidal features [17]. ALS Plus overlap is explained by genetic and pathological convergence with frontotemporal dementia (FTD) and parkinsonian syndromes, with TDP-43 pathology being common across ALS/FTD [18]. Common clinical findings include progressive limb, bulbar, or respiratory weakness, muscle wasting and fasciculations, spasticity, hyperreflexia, and extensor plantar responses [14]. Bulbar involvement manifests as dysarthria, dysphagia, and emotional lability (pseudobulbar affect). Cognitive and behavioral features such as executive dysfunction and personality change are consistent with the ALS-FTD spectrum in a subset of patients [17]. Extrapyramidal and dystonic features including rigidity, tremor, dystonia, and parkinsonian signs are observed in ALS Plus phenotypes [18]. The course is one of rapid functional decline, with variable site of onset; some phenotypes progress over years, while others deteriorate more aggressively [14]. Diagnostic evaluation relies on electrodiagnostics, imaging, biomarkers, and genetic testing. Nerve conduction studies typically show reduced CMAP amplitudes with relatively preserved conduction velocities, while sensory SNAPs remain normal [19]. Electromyography demonstrates active denervation with fibrillations and positive sharp waves, chronic reinnervation with large amplitude and long duration neurogenic motor unit potentials, reduced recruitment, and fasciculations across multiple regions fulfilling diagnostic criteria [19]. MRI brain may reveal corticospinal tract hyperintensities and frontotemporal atrophy in ALS-FTD overlap, though many patients have non-specific or normal MRI findings [20]. Spinal imaging is often unremarkable and is performed to exclude structural mimics. Biomarkers such as CSF or serum neurofilament light chain (NfL) are elevated in many ALS cases, providing supportive but not diagnostic evidence [21]. Pathology demonstrates TDP-43 proteinopathy in most non-SOD1 ALS, though definitive diagnosis is only possible post-mortem or in research biopsy [16]. Genetic testing is used to identify familial forms and characterize ALS Plus phenotypes, with panel testing revealing known ALS genes or overlapping neurodegeneration genes [17]. ALS is universally fatal, typically over months to a few years, although ALS Plus phenotypes may show variable trajectories but remain progressive [14]. Management strategies include disease-modifying therapies such as riluzole and edaravone, which may modestly slow progression in selected patients [22]. Symptom and supportive care are critical, involving multidisciplinary management, nutritional support, non-invasive ventilation, speech and swallow therapy, and spasticity and mood management [23]. Dopaminergic therapy such as syndopa may be used for parkinsonian features, and antiseizure agents like sodium valproate for jerky movements, as in the ALS Plus cases described [23].

7. Summary and Conclusion

ALS must be considered as a potential diagnosis in patients presenting with progressive motor weakness, fasciculations, spasticity, and bulbar or respiratory involvement without evidence of structural, infectious, or metabolic causes. A high index of clinical suspicion for ALS, careful exclusion of differential diagnoses such as neuropathies, myopathies, and metabolic or autoimmune disorders, and appropriate use of available diagnostic tools including neurophysiology (NCS/EMG), MRI, biomarkers, and genetic testing are crucial in accurately and

promptly evaluating a patient with suspected ALS . Given its universally fatal course, early recognition allows timely initiation of disease-modifying therapy, multidisciplinary supportive care, and genetic counseling where appropriate and research in future may bring novel genes association which we have seen in our case series .

8. Bibliography

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9. Tables and Charts

TABLE-1: Shows genes and its association in this case series of ALS.

Gene	Function	Evidence	ALS/ALS-Plus Correlation
PNPLA6	Encodes neuropathy target esterase; crucial for neuronal	Frontiers in Neurology (2022): biallelic PNPLA6 variants cause	Familial ALS-Plus phenotype with dystonia and jerky movements;

Gene	Function	Evidence	ALS/ALS-Plus Correlation
	maintenance and lipid metabolism	spastic paraplegia, ataxia, motor neuron disease	supports motor neuron degeneration
ABCA7	ATP-binding cassette transporter; involved in lipid metabolism and amyloid clearance	Nature Genetics (2015): ABCA7 variants increase Alzheimer's and FTD risk via altered lipid/amyloid processing	ALS-Plus with dementia overlap, especially extrapyramidal and bulbar features
SAMD9L	Sterile alpha motif domain-containing protein 9-like; regulates cell proliferation and antiviral response	Blood (2025): SAMD9L mutations cause ataxia-pancytopenia and multisystem neurodegenerative syndromes	Novel ALS-Parkinson's-Dementia complex in your case; not yet validated in ALS cohorts

10. Figures and Illustration

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PATIENT DETAILS:

Name : MR MANIKNDAN	Referring Physician : Dr. Kalpana
Age : 28 YEARS	Hospital : KGMCH
Gender : I	Place : Kanyakumari
Case Id : 073	
Test Required : WHOLE EXOME SEQUENCING	

SAMPLE DETAILS:

Specimen Type : Peripheral Venous Blood Sample	Approved Date : 29-Jul-2025
Collection Date : 29 Jul 2025	Report Date : 21-Aug-2025
Receipt Date : 30 Jul 2025	Version : I

CLINICAL HISTORY:

Mr Manikandan, a 28-year-old male, presented with weakness of all 4 limbs, slurry of speech, twisted posture of both arms & legs for the past 8 years. The patient also has a history of Jaundice. He is provisionally diagnosed as Familial ALS plus syndrome and is being investigated to find the underlying genetic cause

RESULT SUMMARY

SIGNIFICANT VARIANT LINKED TO THE PHENOTYPE WERE DETECTED

*Recommend correlation with the patient's clinical profile and family history.

SNV DETAILS RELATED TO PHENOTYPE

No	Gene (Transcript ID)	Location	Nucleotide/ Amino acid	Disorder (OMIM)	Inheritance	Zygosity	dbSNP	ACMG Classification
1	NEK1 NM_001199397.3	4:169438103	c.2744A>C p.Lys915Thr	AMYOTROPHIC LATERAL SCLEROSIS, SUSCEPTIBILITY TO, 24; ALS24	Autosomal Dominant	Heterozygous		Uncertain Significance
2	PNPLA6 NM_001166114.2	19:7540279	c.685G>A p.Gly229Arg	SPASTIC PARAPLEGIA 39; BOUCHER-NEUHAUSER SYNDROME BNHS; OLIVER-MCFARLANE SYNDROME; OMCS	Autosomal Recessive	Heterozygous	rs1174515690	Likely Pathogenic

Figure 1-Genetic study of case-1.

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**PATIENT DETAILS:**

Name	: MR SELVAKUMAR	Referring Physician	: Dr. Kalpana
Age	: 49 YEARS	Hospital	: KGMCH
Gender	: MALE	Place	: Kanniyakumari
Case Id	: 078		
Test Required	: WHOLE EXOME SEQUENCING		

SAMPLE DETAILS:

Specimen Type	: Peripheral Venous Blood Sample	Approved Date	: 25-Jul-2025
Collection Date	: 25 Jul 2025	Report Date	: 14-Aug-2025
Receipt Date	: 26 Jul 2025	Version	: 1

CLINICAL HISTORY:

Mr Selvakumar, a 49-year-old male, presented with weakness of all 4 limbs, slurry of speech, muscle atrophy in UL and LL. The patient is provisionally diagnosed as Definitive ALS plus syndrome, ALS-Parkinson's-Dementia complex and is being investigated to find the underlying genetic variations

RESULT SUMMARY**SIGNIFICANT VARIANT LINKED TO THE PHENOTYPE WERE DETECTED**

*Recommend correlation with the patient's clinical profile and family history.

SNV DETAILS RELATED TO PHENOTYPE

No	Gene (Transcript ID)	Location	Nucleotide/ Amino acid	Disorder (OMIM)	Inheritance	Zygosity	dbSNP	ACMG Classification
1	ABCA7 NM_019112.4	19:1055908	c.4208del p.Leu1403ArgfsTer7	ALZHEIMER DISEASE 9, SUSCEPTIBILITY TO: AD9	Autosomal Dominant	Heterozygous	rs538591288	Likely Pathogenic
2	PARK7 NM_007262.5	1:7961850	c.-24+75 - 24+92dup	PARKINSON DISEASE 7, AUTOSOMAL RECESSIVE EARLY- ONSET, PARK7	Autosomal Recessive	Heterozygous	rs200968609	Likely Benign

Figure 2-Genetic study of case 2.

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**PATIENT DETAILS:**

Name	: MR THANGAMANI	Referring Physician	: Dr. Kalpana
Age	: 65 YEARS	Hospital	: KGMCH
Gender	: MALE	Place	: Kanyakumari
Case Id	: 081		
Test Required	: WHOLE EXOME SEQUENCING		

SAMPLE DETAILS:

Specimen Type	: Peripheral Venous Blood Sample	Approved Date	: 28-Jul-2025
Collection Date	: 28 Jul 2025	Report Date	: 20-Aug-2025
Receipt Date	: 29 Jul 2025	Version	: I

CLINICAL HISTORY:

Mr Thangamani, a 65-year-old male, presented with Low back ache, weakness of all 4 limbs, numbness and memory disturbances. The patient is provisionally diagnosed as ALS plus syndrome, Definitive ALS-Parkinson's-Dementia complex and is being investigated to find the underlying genetic variations

RESULT SUMMARY**SIGNIFICANT VARIANT LINKED TO THE PHENOTYPE WERE DETECTED**

*Recommend correlation with the patient's clinical profile and family history.

SNV DETAILS RELATED TO PHENOTYPE

No	Gene (Transcript ID)	Location	Nucleotide/ Amino acid	Disorder (OMIM)	Inheritance	Zygosity	dbSNP	ACMG Classification
1	SAMD9L NM_152703.5	7:93133907	c.2065C>T p.Arg689*	SPINOCEREBELLAR ATAXIA 49; SCA49	Autosomal Dominant	Heterozygous	rs369074740	Likely Pathogenic
2	APOE NM_000041.4	19:44908684	c.388T>C p.Cys130Arg	ALZHEIMER DISEASE 3; AD3 ALZHEIMER DISEASE 2; AD2	Autosomal Dominant	Heterozygous	rs429358	Benign

Figure 3: Genetic study of case 3.