

Co-occurrence of spinocerebellar ataxia type 16 and IDH-mutant oligodendroglioma associated with compound heterozygous STUB1 variants: a case report

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Case Report

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Abstract

Background:

Autosomal recessive spinocerebellar ataxia type 16 (SCAR16), caused by biallelic STUB1 variants, is a rare cerebellar degenerative disorder. While STUB1 (encoding CHIP) is increasingly recognized as a tumor suppressor in gliomas, the co-occurrence of SCAR16 and intracranial glioma has not been systematically reported. This study aims to characterize the clinical, radiological, and genetic features of this unique comorbidity and explore the underlying pathogenic mechanisms.

Case presentation:

We report a 35-year-old woman with a 7-year history of progressive gait ataxia. Initial cranial MRI revealed diffuse cerebellar atrophy. Whole-exome sequencing identified compound heterozygous STUB1 variants: a nonsense mutation (c.352C>T, p.Gln118Ter) and a missense mutation (c.433A>C, p.Lys145Gln), confirmed by familial segregation analysis. At age 33, serial MRI detected a new right temporal lobe lesion. Surgical resection was performed, and histopathology confirmed a WHO grade 2 IDH-mutant oligodendroglioma. Postoperatively, the patient received adjuvant temozolomide chemotherapy.

Conclusions:

This case provides the first clinical evidence linking biallelic STUB1 loss-of-function to both neurodegeneration and gliomagenesis. We propose a dual-pathway model wherein STUB1 deficiency impairs neuronal protein quality control (leading to cerebellar atrophy) and relieves tumor-suppressor restraint in glial cells (increasing susceptibility to IDH-mutant glioma). These findings expand the phenotypic spectrum of STUB1-related disorders and underscore the necessity of genetic screening in adult-onset ataxia with atypical features.

Background

Spinocerebellar ataxias (SCAs) constitute a heterogeneous group of neurodegenerative disorders primarily characterized by progressive cerebellar dysfunction. While traditionally classified into autosomal dominant, recessive, X-linked, and mitochondrial subtypes^[1], the phenotypic spectrum of recessive forms continues to expand. Autosomal recessive spinocerebellar ataxia type 16 (SCAR16), caused by biallelic STUB1 variants encoding the CHIP protein, was first described in 2013^[2]. Due to its low prevalence and often negative family history, SCAR16 is frequently misdiagnosed as multiple system atrophy or sporadic ataxia^[3].

The STUB1-encoded CHIP protein functions as an E3 ubiquitin ligase critical for maintaining neuronal proteostasis. Beyond its neuroprotective role, emerging evidence suggests that STUB1 also acts as a tumor suppressor across various malignancies^[4, 5]. However, clinical evidence linking STUB1 deficiency

to both neurodegeneration and tumorigenesis remains scarce^[6]. Herein, we report the first documented case of SCAR16 comorbid with an IDH-mutant oligodendroglioma. This case expands the phenotypic spectrum of STUB1-related disorders and provides clinical insights into the dual role of CHIP in coordinating protein homeostasis and tumor suppression.

Case Presentation

A 35-year-old Chinese woman presented with a 7-year history of progressive gait instability, which had exacerbated over the past 6 months. She denied any history of trauma, toxin exposure, or relevant family history, and her parents were healthy.

Her symptoms began insidiously at the age of 28 years with difficulty descending stairs. By 2021 (aged 31 years), neurological examination at The First Affiliated Hospital of Xiamen University revealed cerebellar ataxia. Cranial MRI demonstrated cerebellar atrophy, and genetic testing later confirmed compound heterozygous variants in the STUB1 gene, leading to a diagnosis of spinocerebellar ataxia type 16 (SCAR16). Symptomatic treatments, including neurotrophic agents, yielded minimal clinical improvement.

In September 2025 (aged 33 years), the patient complained of worsening dizziness. A follow-up MRI revealed a new space-occupying lesion in the right temporal lobe, highly suspicious for a low-grade glioma. She was subsequently referred to Fujian Medical University Union Hospital and underwent microsurgical resection of the right temporal mass on September 19, 2025. Histopathological examination confirmed an IDH-mutant oligodendroglioma (WHO grade 2). Postoperatively, she received adjuvant temozolomide chemotherapy and rehabilitation training.

Physical examination upon admission to our department revealed a conscious patient with dysarthria. Horizontal nystagmus was noted bilaterally. Cerebellar signs were evident, including dysmetria on finger-to-nose and heel-to-shin tests, as well as dysdiadochokinesia. She exhibited a wide-based gait and was unable to walk tandem. Muscle strength was full (grade 5), and tone was normal. Deep tendon reflexes were brisk (+++), with extensor plantar responses (Pussep sign positive) but no pathological reflexes. Notably, cognitive function and autonomic nervous system examinations were preserved.

Serial imaging confirmed diffuse atrophy of the bilateral cerebellar hemispheres and middle cerebellar peduncles (MCP). The right temporal lesion appeared as a patchy abnormal signal with mass effect (Fig. 1). Histopathology showed morphological features of oligodendroglioma. Immunohistochemistry was positive for IDH1, GFAP, and Olig2, with a low Ki-67 labeling index of approximately 3% (Fig. 2).

Whole-exome sequencing identified compound heterozygous STUB1 variants: a nonsense mutation (c.352C>T, p.Gln118Ter) predicted to cause protein truncation, and a missense mutation (c.433A>C, p.Lys145Gln) affecting a highly conserved functional domain. Familial segregation analysis confirmed the c.352C>T variant in the father and the c.433A>C variant in the mother, both asymptomatic carriers (Fig. 3).

Discussion

To the best of our knowledge, this is the first clinical report demonstrating that biallelic STUB1 loss-of-function may confer susceptibility to both neurodegeneration and gliomagenesis. Although functional validation is required, the current evidence supports a "dual-pathway" pathogenic model (Fig. 4).

Genotype-phenotype correlation analysis revealed that the identified nonsense and missense variants affect both protein truncation and functional domains, consistent with biallelic inactivation. This underlies the early-onset and severe cerebellar atrophy observed in this patient. Notably, the temporal relationship—where a new glioma emerged four years after the SCAR16 diagnosis—strongly argues against coincidental comorbidity, suggesting a shared molecular etiology.

A plausible mechanistic explanation involves the bidirectional regulatory roles of the STUB1-encoded CHIP protein. In neurons, CHIP maintains proteostasis; its deficiency leads to the accumulation of misfolded proteins and subsequent Purkinje cell death, aligning with previous reports on CHIP-related neurodegeneration^[7]. Conversely, in glial cells, CHIP acts as a tumor suppressor by inhibiting the NF- κ B pathway via IKK α degradation. The loss of this restraint likely releases the brakes on glial cell proliferation, thereby increasing glioma susceptibility^[8]. This model is further corroborated by recent studies highlighting the broad tumor-suppressive functions of STUB1^[9, 10].

From a clinical perspective, STUB1 screening should be considered in adult patients with sporadic ataxia, even in the absence of a family history. More importantly, the emergence of an intracranial mass in a patient with a known STUB1 mutation should raise suspicion for a neoplastic process rather than being dismissed as incidental.

The primary limitation of this study is its nature as a single-case report lacking in vitro or in vivo functional assays. Future studies utilizing cell or animal models carrying these specific STUB1 variants are warranted to quantify their differential effects on neuronal survival and glial proliferation.

Conclusions

Biallelic STUB1 variants can lead to typical adult-onset SCAR16 and predispose individuals to low-grade glioma. These findings expand the phenotypic spectrum of STUB1-related disorders, delineating its dual role as both a regulator of neurodegeneration and a tumor suppressor in the central nervous system. Long-term radiological surveillance and systematic genetic counseling for affected families are strongly recommended.

Abbreviations

CHIP: C-terminus of Hsp70 Interacting Protein

MCP: Middle Cerebellar Peduncle

SCAR16: Spinocerebellar Ataxia type 16

WES: Whole Exome Sequencing

IDH: Isocitrate Dehydrogenase

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. The study was reviewed and exempted by the Ethics Committee of Xiamen Hospital of Traditional Chinese Medicine (Exemption No.: 2026-K077-01). Written informed consent to participate was obtained from the patient and her parents.

Consent for publication

Written informed consent for publication of personal and clinical information, including MRI images and the pedigree chart, was obtained from the patient and her parents. A copy of the written consent is available from the corresponding author upon reasonable request.

Data Availability

The raw sequencing data (VCF files) cannot be deposited in public repositories due to restrictions imposed by the clinical diagnostic laboratory. To ensure transparency while protecting patient privacy, we have provided fully anonymised variant summaries and Sanger sequencing validation results as supplementary material. Aggregated anonymised data are available from the corresponding author upon reasonable request and with appropriate ethical approval.

Competing interests

The author declares no competing interests.

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Author's contributions

Youxian Liu: Conceptualization, Data curation, Writing – original draft, Patient care.

Feng-e Zheng: Investigation, Data curation, Manuscript review.

Ling Gao: Genetic analysis, Validation, Manuscript review & editing.

Haipeng Jin: Supervision, Project administration, Funding acquisition, Writing – review & editing.

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References

1. Mylvaganam S, Earnshaw R, Heymann G, Kalia SK, Kalia LV. C-terminus of Hsp70 Interacting Protein (CHIP) and Neurodegeneration: Lessons from the Bench and Bedside. *Curr Neuropharmacol*. 2021;19(7):1038–68. 10.2174/1570159X186662011161455 07.
2. Shi Y, Wang J, Li JD, Ren H, Guan W, He M, Yan W, Zhou Y, Hu Z, Zhang J, Xiao J, Su Z, Dai M, Wang J, Jiang H, Guo J, Zhou Y, Zhang F, Li N, Du J, Xu Q, Hu Y, Pan Q, Shen L, Wang G, Xia K, Zhang Z, Tang B. Identification of CHIP as a novel causative gene for autosomal recessive cerebellar ataxia. *PLoS ONE*. 2013;8(12):e81884. 10.1371/journal.pone.0081884.
3. Synofzik M, Schüle R, Schulze M, Gburek-Augustat J, Schweizer R, Schirmacher A, Krägeloh-Mann I, Gonzalez M, Young P, Züchner S, Schöls L, Bauer P. Phenotype and frequency of STUB1 mutations: next-generation screenings in Caucasian ataxia and spastic paraplegia cohorts. *Orphanet J Rare Dis*. 2014;9:57. 10.1186/1750-1172-9-57.
4. Zhang D, Chen S, Peng W, Liu G, Zhang Q, Ghani MU, Zhou P, Zhao H, Liang P, Cui H. The E3 ubiquitin ligase STUB1 inhibits glioblastoma progression though promoting IKK α ubiquitination and blocking NF- κ B signaling pathway. *Int J Biol Macromol*. 2025;321(Pt 2):146064. 10.1016/j.ijbiomac.2025.146064.
5. Kanack AJ, Newsom OJ, Scaglione KM. Most mutations that cause spinocerebellar ataxia autosomal recessive type 16 (SCAR16) destabilize the protein quality-control E3 ligase CHIP. *J Biol Chem*. 2018;293(8):2735–43. 10.1074/jbc.RA117.000477.
6. Chiu HH, Hsaio CT, Tsai YS, Liao YC, Lee YC, Soong BW. Clinical and Genetic Characterization of Autosomal Recessive Spinocerebellar Ataxia Type 16 (SCAR16) in Taiwan. *Cerebellum*. 2020;19(4):544–9. 10.1007/s12311-020-01136-4.
7. Shi CH, Schisler JC, Rubel CE, Tan S, Song B, McDonough H, Xu L, Portbury AL, Mao CY, True C, Wang RH, Wang QZ, Sun SL, Seminara SB, Patterson C, Xu YM. Ataxia and hypogonadism caused by the loss of ubiquitin ligase activity of the U box protein CHIP. *Hum Mol Genet*. 2014;23(4):1013–24. 10.1093/hmg/ddt497. . Epub 2013 Oct 9.
8. Cao Z, Li G, Shao Q, Yang G, Zheng L, Zhang T, Zhao Y. CHIP: A new modulator of human malignant disorders. *Oncotarget*. 2016;7(20):29864–74. 10.18632/oncotarget.8219.
9. Liu Y, Zhou H, Tang X. STUB1/CHIP: New insights in cancer and immunity. *Biomed Pharmacother*. 2023;165:115190. 10.1016/j.biopha.2023.115190. . Epub 2023 Jul 26.
10. Karmakar S, Chatterjee M, Basu M, Ghosh MK. STUB1 (CHIP) - a prognostic marker in cancer. *Mol Omics*. 2025;21(6):768–93. 10.1039/d5mo00205b.

Figures

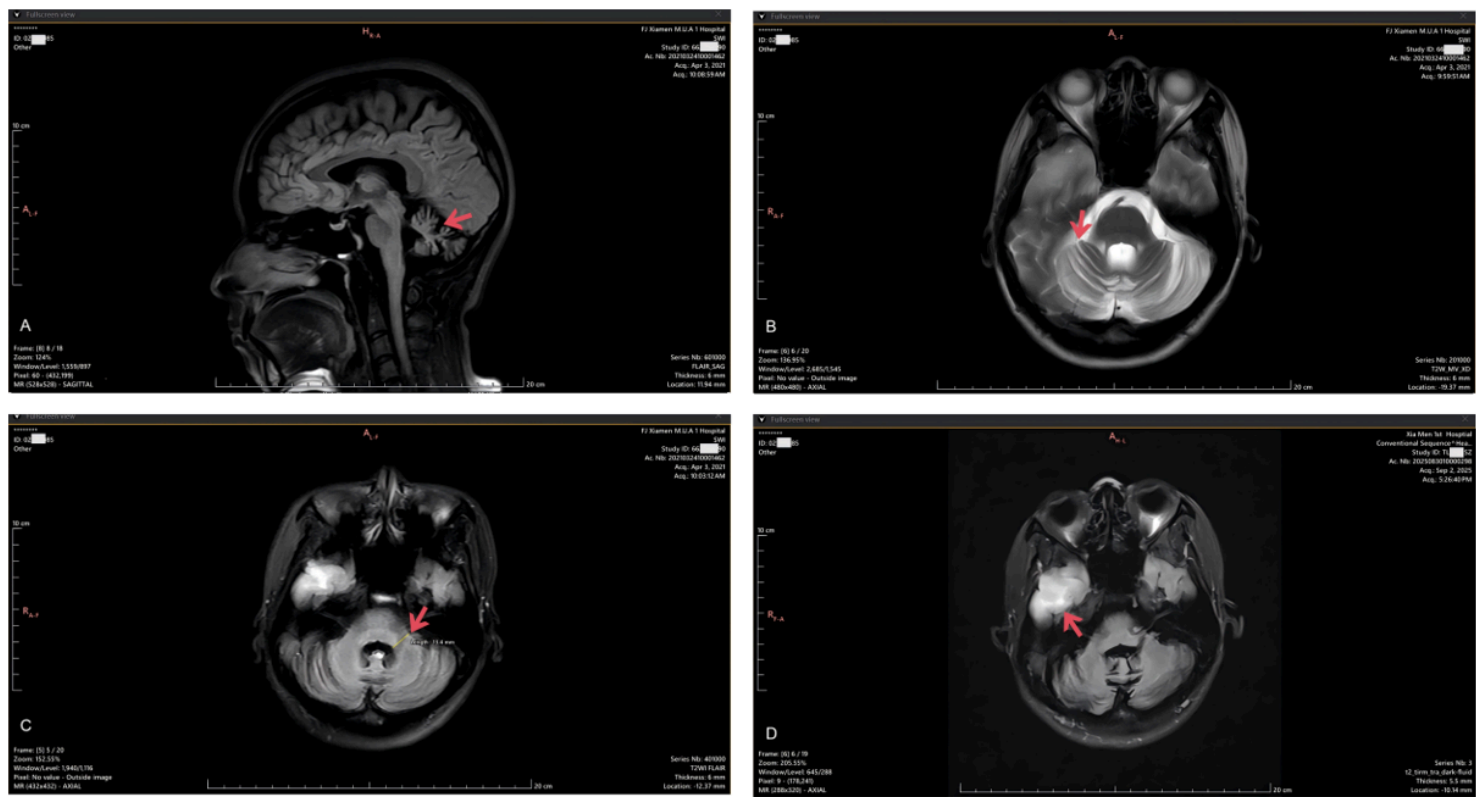


Figure 1

Characteristic neuroimaging features of the patient.

Panel A: Axial FLAIR sequence displaying prominent cerebellar atrophy. Panel B: Axial T2-weighted MRI confirming global cerebellar volume loss. Panel C: Axial T2-weighted image highlighting focal atrophy of the brachium pontis (middle cerebellar peduncle). Panel D: Axial T2-weighted MRI revealing a space-occupying lesion in the right temporal lobe.

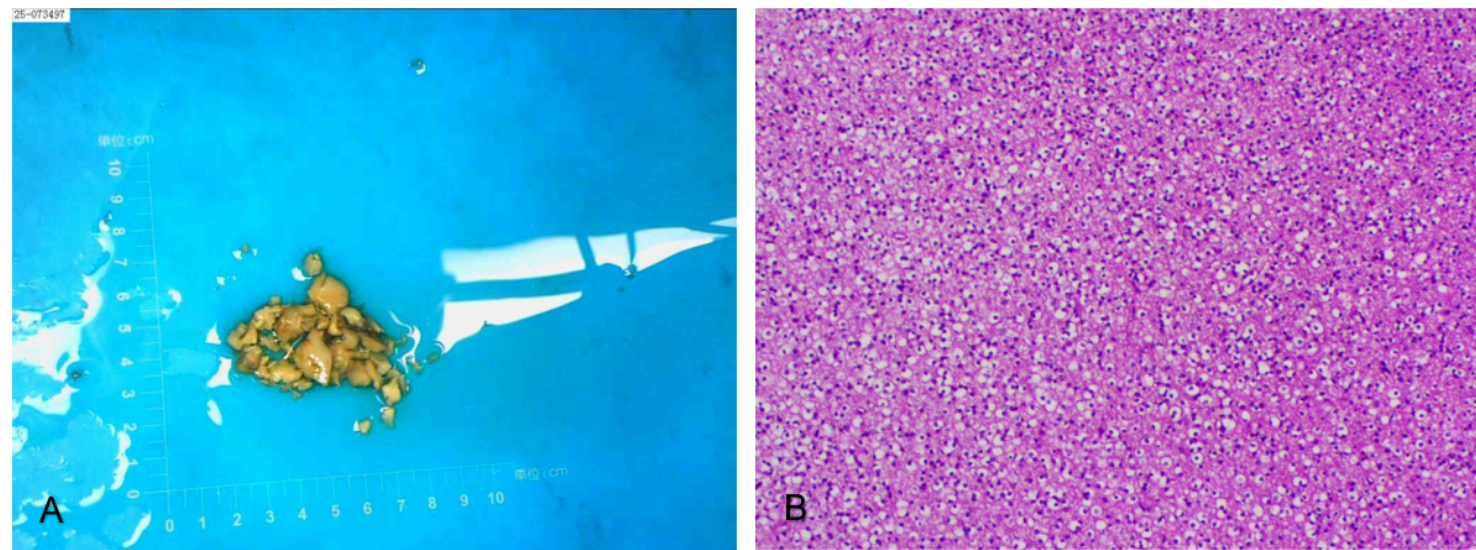


Figure 2

Representative gross and microscopic images of a right temporal lobe glioma (WHO grade 2 oligodendroglioma).

Panel A: Gross appearance of the surgically resected tumor, revealing a discrete, firm, tan-brown mass. Panel B: Histological examination (Hematoxylin and Eosin stain) illustrates a moderately cellular neoplasm composed of glial cells with characteristic round nuclei, fine granular chromatin, and a microcystic background, fulfilling the morphological criteria for WHO grade 2 oligodendroglioma.

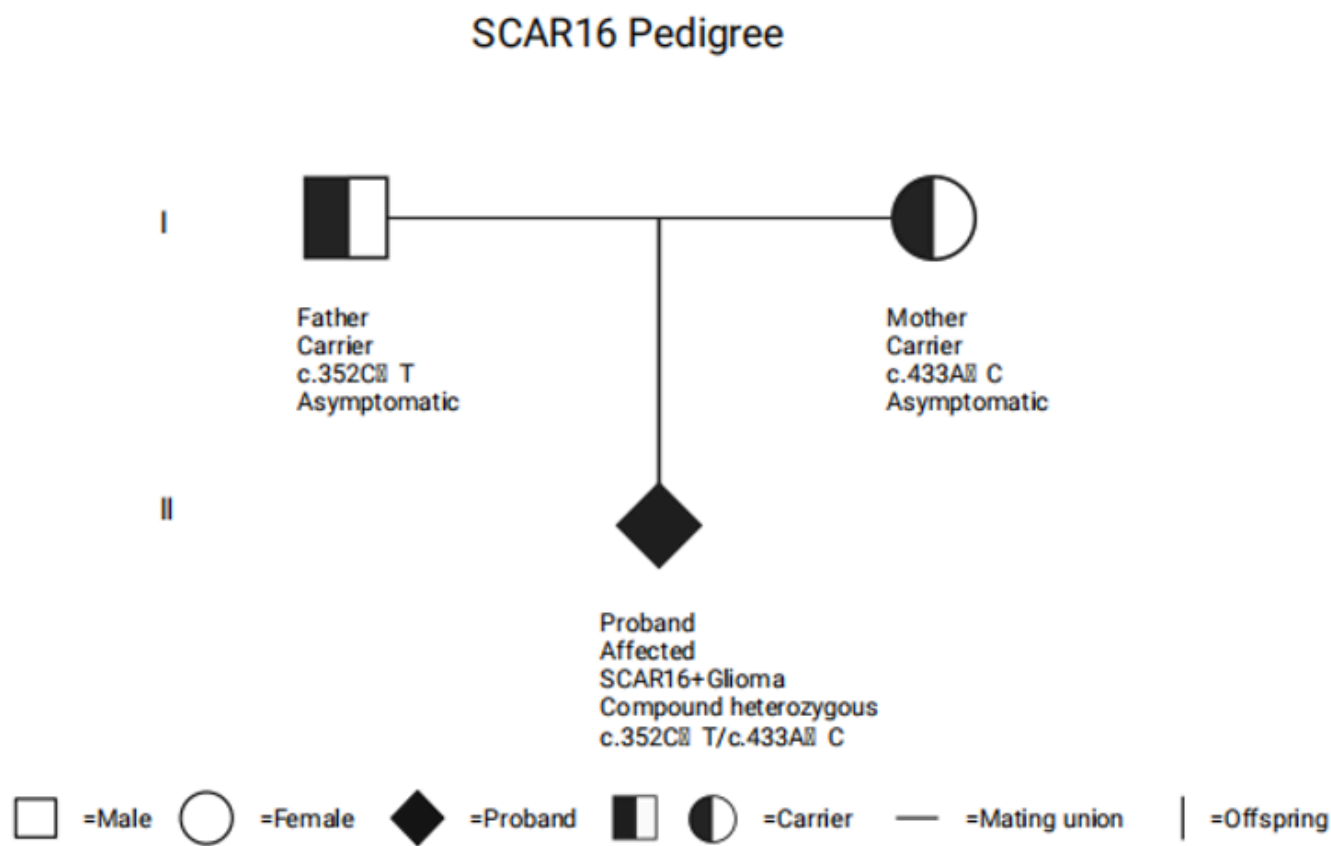


Figure 3

Pedigree of the family with STUB1-related spinocerebellar ataxia type 16 (SCAR16) and oligodendroglioma.

Fig.3 Squares represent males, and circles represent females. The arrow indicates the proband (II-1), who presented with cerebellar ataxia and an IDH-mutant oligodendroglioma. Half-filled symbols denote asymptomatic carriers of STUB1 compound heterozygous variants (c.352C>T and c.433A>C). Solid black

symbols indicate affected individuals. Roman numerals (I, II) represent generations, and Arabic numerals (1, 2) indicate individuals within each generation.

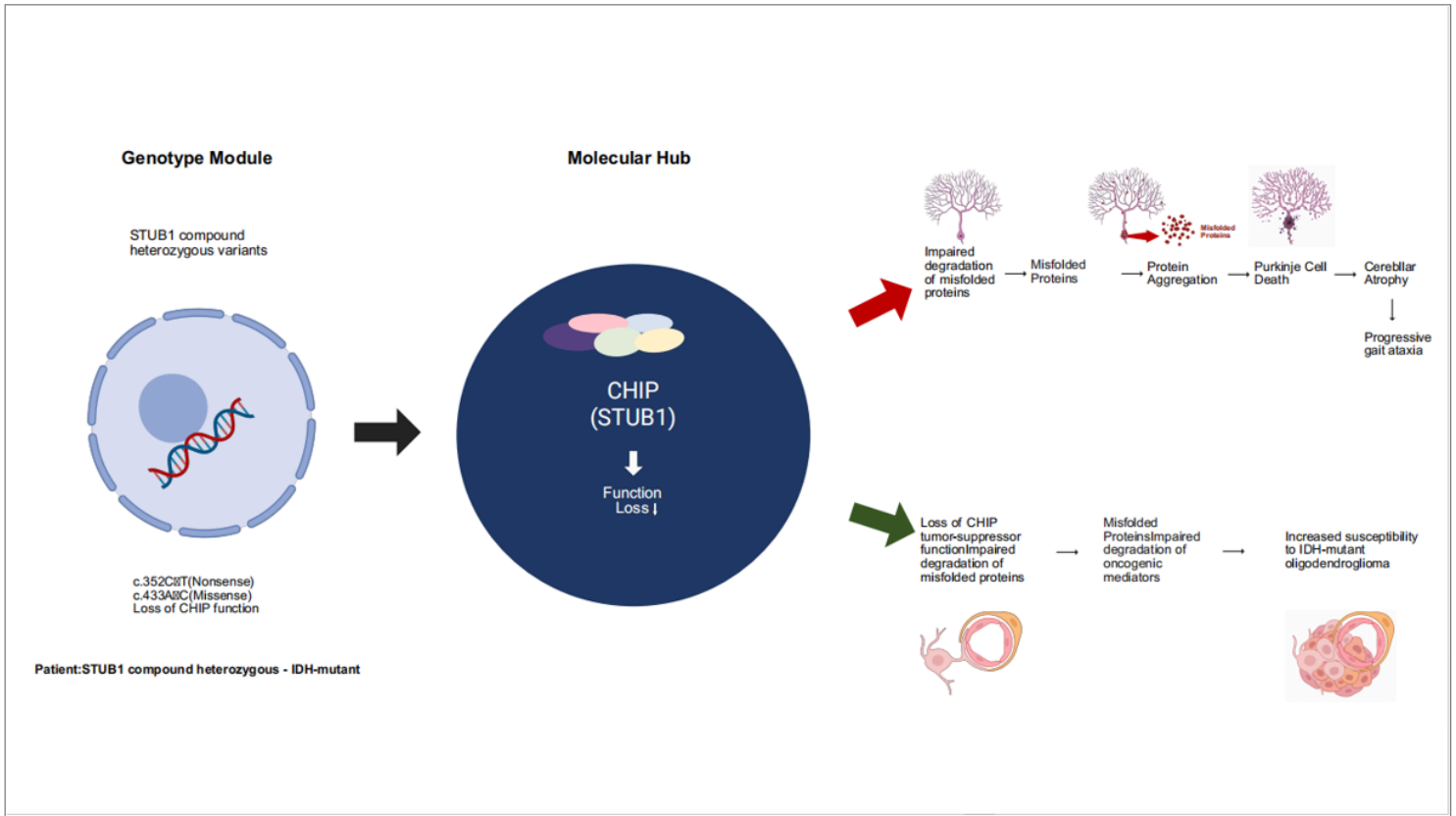


Figure 4

Dual-pathway mechanism of STUB1 deficiency underlying neurodegeneration and gliomagenesis.

Fig.4 (Left) Genetic basis: The patient harbors compound heterozygous truncating variants in STUB1, resulting in a loss of CHIP function. (Center) Molecular hub: This functional impairment acts as the central node driving two distinct pathological processes. (Right) Pathophysiological consequences: (Top, red pathway) In neurons, impaired degradation of misfolded proteins leads to protein aggregation, Purkinje cell apoptosis, and subsequent cerebellar atrophy. (Bottom, green pathway) In glial cells, the loss of CHIP-mediated tumor suppression disrupts proteostasis and activates oncogenic mediators, increasing susceptibility to IDH-mutant oligodendroglioma.

Supplementary Files

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- [VideoofUnsteadyGait.mp4](#)