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Original article

SETD1B variants associated with absence seizures

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ABSTRACT

Aim: Exploring the association between *SETD1B* variants and absence seizures (ASs).
Methods: We engaged a small cohort of four pediatric epilepsy patients with identified *SETD1B* variants and conducted a comprehensive review of 50 documented instances. Clinical profiles were meticulously compiled, and genetic screening was executed via trio-based whole-exome sequencing. Our literature survey centered on AS manifestations linked to *SETD1B* alterations, utilizing descriptive statistics for analysis.
Results: The quartet of new cases presented with developmental impediments, cognitive deficits, and epileptic manifestations. Pathogenicity was established in the detected *SETD1B* variants. Among the 54 individuals, 26 (accounting for 48.1 %) presented with AS during the course of the disease. The median seizure onset age stood at 44.8 months, with a majority displaying cognitive challenges and autistic traits. Anti-epileptic drug therapies proved efficacious in 70.8 % of the instances. Notably, variants within the N-SET, SET, and post-SET domains of *SETD1B* were prevalent in 46.2 % of the AS-afflicted cohort.
Discussion: Our findings accentuate the potential influence of *SETD1B* variants in AS pathogenesis, these variants may perturb neuronal excitability, possibly via modulation of histone methylation landscapes. The insights garnered here deepen our grasp of AS's genetic architecture.
Conclusion: Our study identified four novel *SETD1B* variants, highlighting that the importance of AS as part of the phenotype among individuals with *SETD1B*, demonstrated by 3 novel cases, and supported by review of the literature. Our findings also suggest that the SET domains may play a potential role in the pathogenesis of AS, providing a clue for future mechanistic research.

1. Introduction

Absence seizures (ASs) mainly occur in children and adolescents, characterized by sudden loss or reduction of consciousness, lasting from a few seconds to tens of seconds, sometimes accompanied by mild motor phenomena such as eye tremors, blinking, or facial muscle twitching [1,2]. These generalized non-convulsive seizures are diagnosed mainly by clinical observation and electroencephalogram (EEG) examination, which shows generalized spike-wave discharges [3,4].

SETD1B encodes a histone methyltransferase, which is involved in chromatin remodeling and gene expression regulation [5,6]. The SETD1B protein consists of several functional domains, including an RNA recognition motif (RRM) at the N-terminus, long disordered regions in the middle region, and a catalytic SET domain, which is bordered by an N-SET domain and a post-SET domain at the C-terminus [7]. Pathogenic *de novo* variants in *SETD1B* have been associated with intellectual disability, autism spectrum disorder, and epilepsy [5,7]. In recent years, several patients with AS carrying *SETD1B* variants have been reported [5–8], which suggests that *SETD1B* may be a possible cause of AS. However, there is still a lack of systematic research on the role and mechanism of *SETD1B* in AS.

In this study, we described a cohort of four previously unreported cases and reviewed 50 published cases with the aim of revealing the association between *SETD1B* and AS.

2. Methods

2.1. Previously unpublished cohort

We enrolled four children with epilepsy and *SETD1B* variants who visited the pediatric department of Peking University People's Hospital from September 2021 to December 2023. We collected the clinical data

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of all four patients using a genetic epilepsy registration form, which included the child's gender, current age, age of seizure onset, seizure type, clinical manifestations, developmental milestones, perinatal status, family history, EEG, brain magnetic resonance imaging (MRI), and treatment. Patients were followed up every six months in the pediatric neurology clinic or by telephone.

Seizure types and epilepsy syndromes were classified according to the International League Against Epilepsy (ILAE) classification criteria [9–13]. AS were further classified into four subtypes—typical absence, atypical absence, absence with or without eyelid myoclonia, and myoclonic absence—based on clinical features and EEG examination results.

Variant screening of *SETD1B* was performed using trio-based whole-exome sequencing (WES), and all variants were described using the transcript NM_001353345.2(GRCh38). We predicted the functional consequences of the variants by Polyphen-2, MutationTaster, and SIFT. The pathogenicity of the variants was interpreted according to the American College of Medical Genetics (ACMG) guidelines [14].

All cases in this study obtained informed consent from themselves or their guardians, and the protocol of this study was also approved by the Ethics Committee of Peking University People's Hospital (approval number: 2023PHB245-001).

2.2. Literature review

We searched the PubMed database up to November 27, 2023, for published literature on AS cases with *SETD1B* variants, using the keywords "*SETD1B*" and "absence seizures" or "epilepsy". Relevant literature was selected through screening of titles and abstracts, followed by full-text review for detailed information. Articles meeting our criteria were examined, excluding those that did not report individual phenotype-genotype patient information or lacked an English version. After cross-checking the data to exclude duplicates, relevant information on *SETD1B* cases was included.

To explore the clinical and genetic characteristics of the AS group in *SETD1B* cases, we further filtered cases that had experienced AS during their course of epilepsy.

Inclusion Criteria: 1) For cases derived from literature: Based on the authors' reports on seizure types and the review of EEG results (if available), cases with absence seizures during the course of the disease will be included. 2) For novel patients in this study: The AS were identified by video EEG with synchronous polyelectromyography monitoring. **Exclusion Criteria:** 1) Cases without a history of AS, and 2) Cases lacking information on seizure type. According to the ILAE guidelines [10–13], the patient's age of onset, seizure types, EEG, and developmental status were assessed to further diagnose possible epilepsy syndromes.

2.3. Statistical analysis

Descriptive statistics were used to analyze the data. Normally distributed variables were described using means, while medians were utilized for those not conforming to a normal distribution. SPSS 25.0 software was used for data analysis.

3. Results

3.1. Epileptic phenotype

In this study we identified four novel patients, who were all females, presented with developmental delay, intellectual disability, and epilepsy (shown in Supplementary Table S2).

Patient 1, at the age of 4 years and 2 months, initiated with a triad of seizure types: myoclonic and atypical absence seizures, which manifested with recurrent episodes occurring dozens of times per hour. Ictal EEG showed 1.5–2.5Hz generalized polyspike-wave (indicating myoclonic seizure) and generalized spike-wave discharges (GSWD; indicating atypical absence seizures). Brain MRI scan came back with normal findings. Treatment with valproic acid and clonazepam proved to be efficacious, successfully managing her seizures. Developmental and epileptic encephalopathy (DEE) was the final diagnosis for the patient, who had moderate developmental delay before and after the onset of seizures.

Patient 2, at the age of 3 years and 6 months, initially presenting as eyelid myoclonia with absence, which became more frequent with emotional excitement. Over time, the seizures progressed to atypical absence. At the age of 6, ictal EEG captured 2–2.5Hz generalized spike-wave discharges (as depicted in Fig. 1-A), indicating atypical absence. Brain MRI scan unveiled abnormal signals in the white matter of the bilateral frontal lobes, hinting at a possible myelin development deficiency. Despite being treated with a regimen of valproic acid, lamotrigine, and zonisamide, the seizures remained poorly controlled. Astonishingly, at the age of 7 years and 8 months, she experienced a spontaneous remission of her seizures, a remarkable occurrence that transpired without any alterations to her anti-seizure medication regimen. DEE was the final diagnosis for the patient, who exhibited developmental regression and moderate developmental delay.

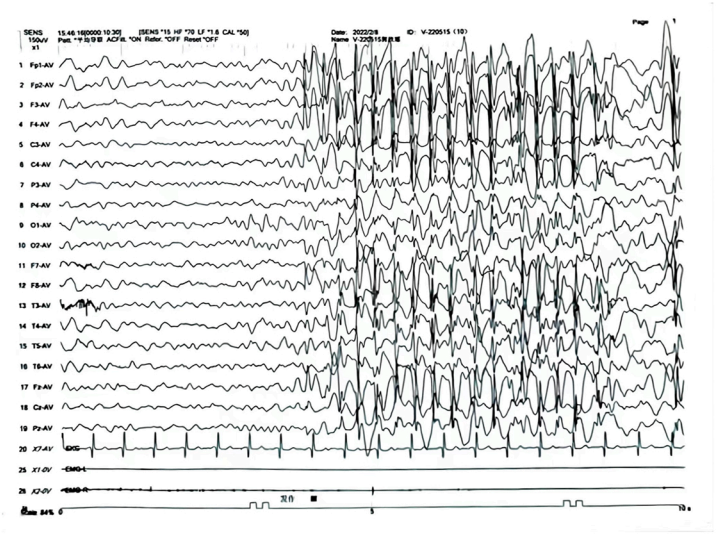
Patient 3, at the age of 1 year and 6 months, initially presenting as typical absence, occasionally accompanied by eyelid myoclonia. Ictal EEG showed 3Hz GSWD (as depicted in Fig. 1-B), indicating typical absence seizures. The patient exhibited a favorable response to a therapeutic regimen consisting of valproic acid and lamotrigine, achieving effective seizure control. Early onset absence epilepsy (EOAE) was the final diagnosis for the patient, who had mild developmental delays before and after the onset of seizures.

Patient 4 did not exhibit AS; instead, at 1 year and 6 months, she began experiencing sporadic mild twitching episodes. However, due to a paucity of detailed clinical information, the specific type of seizure could not be ascertained. Subsequently, at the age of 3, the patient manifested atonic seizures characterized by head nodding and single drops, occurring once per hour and with increased frequency during periods of emotional distress. Ictal EEG revealed generalized discharges, indicating atonic seizures. Brain MRI yielded normal findings. The seizures were controlled with the administration of valproic acid. However, during a telephone follow-up at the age of 7 years and 4 months, the parents reported a reduction in the dosage of valproic acid due to alopecia, which led to occasional mild upper limb twitching (the type of seizure remains undetermined due to the absence of video and EEG data). Further investigation is required to determine whether the patient's condition fits any established epilepsy syndrome.

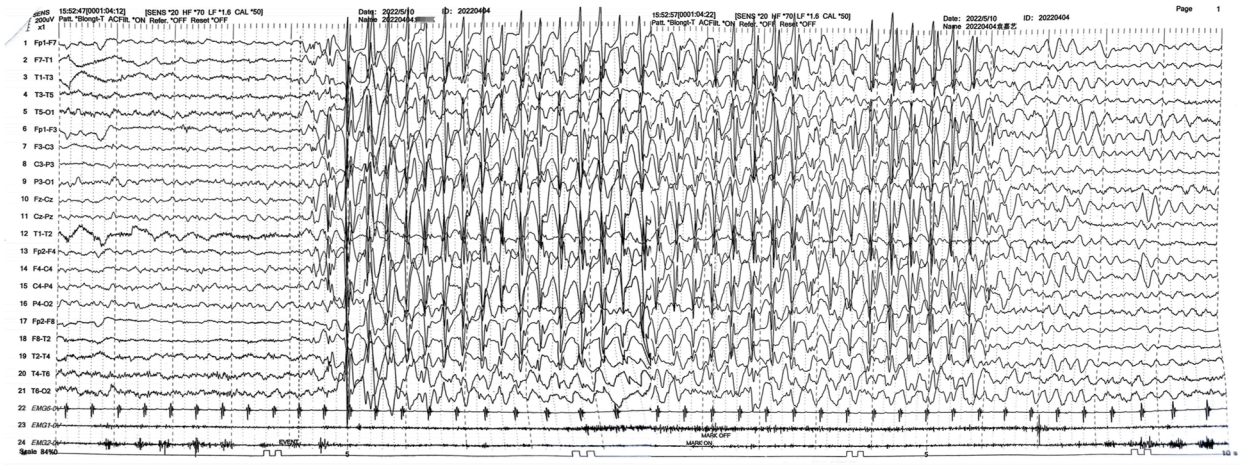
We have compiled data on 50 individuals with *SETD1B* variants as reported in the literature [5–8,15–17]. Supplementary Table S1 presents a comprehensive overview of the variant sites and seizure types across 54 cases, comprising 50 cases from existing literature and an additional four from this study. Of these, 26 cases—23 sourced from the literature and three from this study—experienced AS during the course of the disease. A separate group of 28 cases, consisting of 27 from the literature and one from this study, presented with other seizure types but not AS. Furthermore, seizure type data was unavailable for 10 cases derived from the literature.

Table 1 summarizes the clinical characteristics of 26 patients primarily presenting with AS. The ratio of females to males is 11:15. The median age at first seizure is 36 months (interquartile ranges from 24 to 49 months). The observed seizure types included absence (n = 26), myoclonic (n = 5), atonic (n = 2), generalized tonic-clonic (n = 7), and focal (n = 7) seizures.

Classification of absence seizures revealed the following distribution: unclassifiable absence in 50 %, typical absence in 3.8 %, atypical absence in 15.4 %, myoclonic absence in 19.2 %, and eyelid myoclonia with or without absence in 23.1 % of cases (n = 26). Classifying 26 patients by epilepsy syndrome, we identified 2 patients presenting with EOAE, 1 with EMA, 1 with LGS, 1 with PME, 2 with DEE, and 19 with



(A) Patient 2



(B) Patient 3

Fig. 1. The ictal EEG patterns for patient 2 and patient 3.**(A)** Patient 2's ictal EEG presents 2.5Hz generalized irregular spike-wave discharge with atypical absence seizure lasting 5 s. **(B)** Patient 3's ictal EEG presents 3Hz generalized spike-wave discharge with typical absence seizure lasting 12 s.

unclassified epilepsy syndrome. Treatment response was effective in 70.8 % (17/24) of cases, with VPA being the most frequently used and effective drug in 11 cases (9 responsive cases).

3.2. Auxiliary clinical phenotypes including development and autism tendencies

The auxiliary clinical phenotypes of four novel patients in this study are detailed in Supplementary Table S2, where it is observed that all patients exhibited delays in language and motor development. The severity of intellectual disability varied, with difficulties observed in logical thinking and attention. Patient 2 presented with pes planus and hypotonia. In terms of family history, aside from patient 3, whose brother and maternal grandfather had a history of febrile seizures, the remaining patients showed no significant familial history of neurological disorders.

Among the 26 patients with AS, the classification of intellectual disability severity revealed that 4.3 % (1/23) had profound impairment, 26.1 % (6/23) had moderate disability, and 52.2 % (12/23) had mild intellectual disability. For 13 % (3/23), the severity of intellectual disability remained undetermined, and in 4.3 % (3/23), no intellectual disability was detected. The median age for the utterance of the first word was 24 months (interquartile ranges from 12 to 30 months). Furthermore, the median age for achieving independent walking was 18 months (interquartile range of 12.5–20 months). A significant proportion, 68 % (17/25), demonstrated autism spectrum traits, in contrast to 32 % (8/25) who did not exhibit such tendencies.

3.3. Genetic analysis

In this study, we identified four novel nonsense variants in the *SETD1B*: c.4516dup (p. Ala1506Glyfs*61) in patient 1, c.1362_1369dup (p. Pro457Argfs*54) in patient 2, c.4781del (p. Pro1594Hisfs*6) in patient 3, and c.3202dup (p. Glu1068Glyfs*37) in patient 4. These variants are classified as pathogenic.

We retrieved data from the literature on 43 *SETD1B* variants carried by 50 patients [5–8,15–17]. Among these variants, missense variants accounted for 69.8 % (30/43), while nonsense variants constituted 30.2 % (13/43). 37.2 % (16/43) of the variants were located within the N-SET, SET, and post-SET domains (SETs; residues 1679–1962), while the remaining 62.8 % (27/43) were distributed in other regions.

Fig. 2 depicts the 26 variant sites in the 26 patients with AS. The ratio of truncating to missense variants is noted as 9:17. Notably, 46.2 % (12/26) of these variants are localized within the SETs, consisting of two

Table 1
Clinical features of the 26 patients with absence seizure.

	ID	Sex	SETD1B variant	Age at First Seizure	Seizure type at onset (seizures of course)	Response to treatment	Intellectual disability (tested IQ)	Language development (age at first word)	Motor development (age at first walking)	Autism/ autistic behavior	Epilepsy syndrome
This study	patient1	female	c.4516dup (p. Ala1506Glyfs*61)	4y 2mo	myoclonic and atypical absence	Yes (VPA and CZP)	Moderate (N/A)	Delayed (2y 6mo)	Delayed (1y)	No	DEE
	patient2	female	c.1362_1369dup (p. Pro457Argfs*54)	3y 4mo	eyelid myoclonia with absence (atypical absence)	No (VPA, LTG and ZNS)	Moderate (N/A)	Delayed(1y)	Delayed (1y 2mo)	Yes	DEE
	patient3	female	c.4781del (p. Pro1594Hisfs*6)	1y 6mo	typical absence	Yes (VPA and LTG)	Mild (N/A)	Delayed(10mo)	Delayed (1y 6mo)	No	EOAE
2018 Hiraide, T. et al.	case1	female	c.5524C > T (p. Arg1842Trp)	2y 9mo	myoclonia (myoclonic absence)	Yes(Seizure free from 6 years)	Mild (64)	Delayed (1y 3mo)	Delayed (1y 8mo)	Yes	/
2019 Hiraide, T. et al.	case1	male	c.386T > G (p.Val129Gly)	3y 7mo	myoclonic absence	No (Daily seizure with VPA and LTG)	Mild (64)	Delayed (2y3mo, short sentences)	N/A	Yes	EMA
2019 Krzyzewska, I. M. et al.	case2	male	p.Arg1902Cys	N/A	absence (tonic-clonic)	N/A	Mild (N/A)	Delayed (N/A)	Normal	No	/
2021 Roston, A. et al.	case1	male	c.5589+1G > A	2y 6mo	eyelid myoclonia (absence)	Yes, partly (ESX)	Moderate (N/A)	Delayed (3y6mo, short sentences)	Delayed (1y 3mo)	No	/
	case3	male	c.5833T > P (p. Phe1945Leu)	2y 6mo	absence, myoclonic absence	Yes (VPA)	N/A	Delayed (2y 3mo)	Delayed (1y 6mo)	Yes	/
	case4	male	c.2932C > T (p.Gln978Ter)	2y 6mo	absence (myoclonia)	N/A (LTG)	Moderate (N/A)	Normal	Delayed (1y 4mo)	N/A	/
2021 Weerts, M. J. A. et al.	case1	male	c.22dup (p.His8fs)	6y	myoclonic absence (generalized tonic-clonic)	Yes (LEV)	Mild (57)	Delayed (2y 1mo)	Delayed (1y 7mo)	Yes (but does not meet ASD criteria)	/
	case7	male	c.337_363inv (p. Asn113_Asp121delins9)	1y	myoclonia and absence	Yes	Mild (77)	Delayed (N/A)	Delayed (1y 8mo)	Yes	/
	case8	female	c.509T > C (p.Met170Thr)	3y	atypical absence (generalized tonic-clonic)	No	Yes (N/A)	Delayed (3y)	Delayed (N/A)	Yes	/
	case11	male	c.953C > T (p.Thr318Met)	10y	generalized tonic-clonic (status epilepticus, absences)	Yes (CBZ, PHT and VPA)	Yes (N/A)	Delayed (no phrases when 14y)	Delayed (3y)	Yes	/
	case15	male	c.1634C > G (p.Pro545Arg)	6y	absence	Yes (LEV and VPA)	Mild (62)	Delayed (1y 6mo)	Delayed (1y 1mo)	Yes	/
	case18	female	c.2945G > A (p.Arg982Gln)	1y	atonic (eyelid myoclonia, absence, tonic)	No	Moderate (41)	Delayed (limited speech)	Normal (1y)	Yes	/
	case21	female	c.3985C > T (p.Arg1329*)	2y	eyelid myoclonia (myoclonia)	No	N/A	Delayed (1y)	Delayed (1y 2mo)	No	PME
	case22	female	c.4271G > A (p. Arg1424Gln)	3y	absence with eyelid myoclonia	Yes (VPA)	Severe (N/A)	Delayed (non-verbal)	Delayed (3y)	No	/
	case24	male	c.4996C > T (p.Gln1666*)	6y	absence and focal	Yes, partly (VNS and CBD)	Mild (69)	Delayed (1y 3mo)	Delayed (1y 5mo)	Yes	/
	case25	male	c.5184_5185del (p. Ala1730*)	3y	myoclonic (eyelid myoclonia)	Yes (VPA and CZP)	No (N/A)	Delayed (6mo)	Delayed (1y)	No	/
	case26	male	c.5242C > T (p. Arg1748Cys)	9y	absence	No	Mild (60–70)	Delayed (N/A)	Normal (1y)	Yes	/
	case27	female	c.5374C > T (p. Arg1792Trp)	6mo	absence (generalized tonic-clonic)	Yes, partly (ESX, TPM)	Mild (N/A)	Delayed (2y) (short sentences)	Delayed (1y 8mo)	Yes (but does not meet ASD criteria)	/
	case28	female	c.5474G > C (p. Arg1825Pro)	4y	absence	Yes	N/A	Delayed (N/A)	Delayed (2y)	No	/

(*continued on next page*)

Table 1 (*continued*)

	ID	Sex	SETD1B variant	Age at First Seizure	Seizure type at onset (seizures of course)	Response to treatment	Intellectual disability (tested IQ)	Language development (age at first word)	Motor development (age at first walking)	Autism/ autistic behavior	Epilepsy syndrome
	case29	female	c.5480A > G (p.Lys1827Arg)	11y	absence (tonic-clonic)	Yes (LTG)	Moderate (47)	Delayed (2y)	Delayed (4y 6mo)	Yes	/
	case32	male	c.5820_5826del (Tyr1941Ilefs*101)	1y	atypical absence, myoclonic absence (Lennox-Gastaut syndrome)	No	Yes (N/A)	Delayed (2y 6mo)	Delayed (1y 8mo)	Yes	LGS
	case35	male	c.5842G > A (p.Glu1948Lys)	2y	absence (absence-atonic/myoclonic, generalized tonic-clonic)	Yes, partly (ESX, VPA, CLB, LTG and DZP)	mild (N/A)	Delayed (2y)	Delayed (2y)	Yes	/
2022 Weng, R. et al.	case1	male	c.5699A > G (p.Tyr1900Cys)	2y	absence (generalized tonic-clonic)	Yes(ESX, VPA, STM and CLB)	mild (N/A)	Delayed (after 2y)	Delayed (1y 6mo)	Yes	EOAE

VPA=Valproic acid; LEV = Levetiracetam; LTG = Lamotrigine; CZP=Clonazepam; ZNS = Zonisamide; ESX = Ethosuximide; LVT = Levetiracetam; TPM = Topiramate; CBZ = Carbamazepine; CLB =Clobazam; STM= Sulthiame; DZP = Diazepam; CBD= Cannabidiol; VNS=Vagus nerve stimulation; PHT= Phenytoin; EOAE = Early onset absence epilepsy; CAE=Children absence epilepsy; EMA = Epilepsy with myoclonic absences; PME=Progressive myoclonus epilepsies; LGS = Lennox-Gastaut Syndrome; DEE = Developmental and Epileptic Encephalopathy; GGE = Genetic generalized epilepsies; N/A = not available.

truncating and ten missense variants. In contrast, 53.8 % (14/26) are distributed in other regions, with seven truncating and seven missense variants, respectively.

4. Discussions

The pathophysiology of AS is related to the excessive excitation of the thalamocortical network, and is widely considered to be polygenic inherited. And some associations with single gene variants have also been found, such as *CACNA1A, SCN1A, SCN8A, HCN1, KCNMA1, GABRG2, CLCN2, SLC2A1*, *SLC6A1* etc [18–26]. *SETD1B* regulates expression of genes characterized by broad histone 3 lysine 4 trimethylation (H3K4me3) peaks at transcription start sites and is closely related to cortical development, neuronal function, and learning behavior. In this study, we found that 48.1 % of cases (26/54) experienced AS during the disease course, suggesting that AS is a significant phenotype in patients with *SETD1B* variants.

Concerning the timing of epileptic seizures, the median age at first seizure for the absence seizure group was 36 months. In addition, two patients were classified as EOAE. These serve as a reminder that genetic causes should be ruled out in EOAE, as previously research mentioned, GLUT1 deficiency caused by *SLC2A1*, which occurs in approximately 10 % of EOAE patients [27]. However, the prevalence of *SETD1B* in the population with EOAE may not be as high as that of *SLC2A1*, and further research is needed to determine its exact frequency.

The classification of AS into subtypes, unclassified absence was most common, followed by eyelid myoclonia with or without absence, myoclonic absence, atypical absence, and typical absence. This finding further refines our understanding of the phenotypic spectrum associated with *SETD1B* variants. The high percentage of unclassifiable absence (50 %) may indicate the complexity of seizure semiology in this patient population or potential limitations in current classification systems. This also implies that future researchers should endeavor to categorize AS into specific subtypes when reporting, to facilitate a more profound analysis of the relationship between *SETD1B* variants and seizure types.

Similarly, it is regrettable that direct reports on epilepsy syndromes within the existing literatures were relatively scarce. However, we can infer possible syndromes from the clinical information provided in publications. Among the 23 AS cases from the literature, 10 cases with significant cognitive impairment before onset were inclined to be diagnosed with DEE, and 9 cases with mild or no developmental disability before onset were inclined to be diagnosed with GGE. Among the three novel AS patients in this study, 2 were diagnosed with DEE (Patient 1 and Patient 2), and 1 was diagnosed with GGE (Patient 3 with EOAE). Comparing the response rates of patients with DEE and GGE to ASMs, the GGE group (80 %) was slightly higher than the DEE group (66.7 %). Of course, due to the lack of primary data to ascertain the syndromes of patients derived from literature, this conclusion has its limitations.

In the context of developmental delays, no significant distinction was observed between individuals with AS and the broader cohort [7] possessing *SETD1B* variants. This suggests that such developmental issues are predominantly associated with underlying genetic factors rather than being a consequence of seizure disorders like AS.

In this study, we identified a hotspot region of variation in the AS group, with 46.2 % (12/26) exhibiting variants located within the SET-associated domains. Additionally, we observed a higher incidence of missense variants in this region compared to others, suggesting a heightened degree of evolutionary conservation and a critical biological function. The SET domain is a crucial catalytic region responsible for transferring methyl groups from donor molecules to substrate molecules, thereby altering the activity or stability of the substrate molecules [7]. Variations in the N-SET, SET, and post-SET domains may affect their catalytic activity or substrate specificity, leading to a decrease in H3K4me3 expression, downregulation of downstream epilepsy risk genes, and consequent alterations in neuronal excitability, ultimately

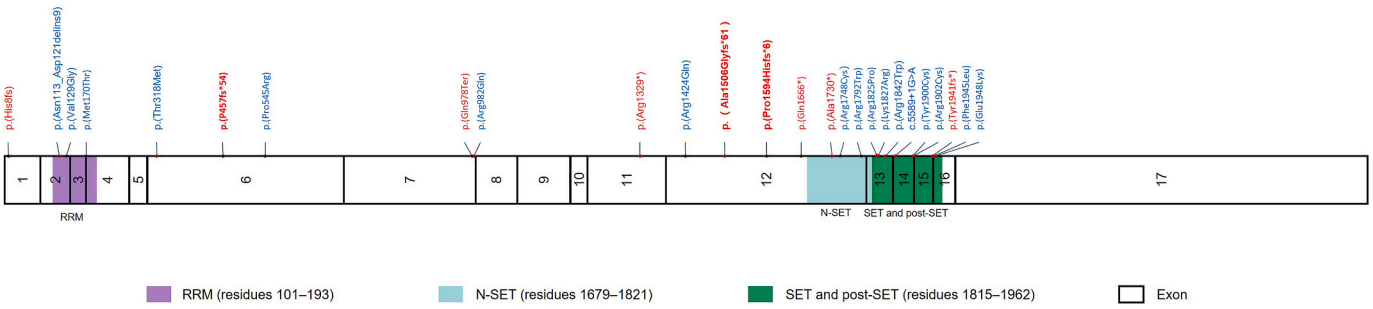


Fig. 2. The location of domains and variants (patients with AS) in SETD1B proteins. Red font indicates truncating variants, blue font indicates missense variants, bold font indicates novel variants in this study. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

resulting in AS.

ASH1L encodes a histone methyltransferase with similar function to *SETD1B*, also regulating H3K4me3 expression and associated with autism phenotypes. Research indicated that changes in synaptic gene expression in the prefrontal cortex might also be a significant factor in epilepsy and autism phenotypes [28,29]. Lack of *ASH1L* in the mouse prefrontal cortex significantly reduced H3K4me3 levels, leading to weakened GABAergic inhibition and altered synaptic gene expression, resulting in excitatory/inhibitory imbalance and seizures [28]. These findings from similar gene imply that the regulation of synaptic gene expression in the prefrontal cortex may underlie the pathogenic mechanisms associated with *SETD1B*-related disorders.

However, the above mechanisms require further experimental validation. Additionally, other influencing factors such as environmental and genetic backgrounds exist. A significant limitation is that, based on the literature review, classifying absence seizures and their subtypes can be challenging, and some patients lack EEG data for review. Future research directions involve conducting deeper genetic and functional analyses, and establishing and validating animal and cell models.

5. Conclusions

In conclusion, our study identified four novel *SETD1B* variants, highlighting that the importance of AS as part of the phenotype among individuals with *SETD1B*, demonstrated by 3 novel cases, and supported by review of the literature. Our findings also suggest that the SET domains may play a potential role in the pathogenesis of absence seizures, providing a clue for future mechanistic research.

Data availability statement

The datasets supporting the current study have not been deposited in a public repository because data are not public but are available from the corresponding author on request.

Declaration of competing interest

Declaration of competing interest: none of the authors has any conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2024.12.002.

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