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Clinical, Behavioral and Neuroradiological Phenotype in an Italian Cohort of Patients With Xia Gibbs Syndrome: A Multicenter Cross-Sectional Study and Systematic Literature Review

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ABSTRACT

Heterozygous variants in the AHDC1 gene are associated with Xia Gibbs Syndrome (XGS), a genetic disorder with a highly variable phenotype. Cognitive impairment, motor delay, language delay, neonatal hypotonia, and sleep apnea are considered "cardinal" signs of the disease. In a multicenter cross-sectional study, we analyzed the genetic, epileptological, behavioral, and neuroradiological features of 15 patients with XGS harboring heterozygous variants in AHDC1. The phenotype of our patient cohort is almost overlapping with that already reported in the literature. Seizures begin between 2 and 9 years, while EEG is generally characterized by normal background activity with paroxysmal abnormalities in the posterior areas increased by sleep. We systematically analyzed brain imaging findings as the most frequent brain alteration: the thinning of the corpus callosum, followed by posterior fossa malformation and lateral ventricle morphology abnormalities. Regarding psychiatric disorders, we observed neurodevelopmental disorders such as ID, language disorders, Autism spectrum disorders (ASD), and ADHD in preschoolers, followed by a prevalence of externalizing problems during childhood and adolescence. Our study showed that epilepsy and brain anomalies are very common among XGS individuals. MRI changes are nonspecific, but their association with other clinical features of the syndrome can guide early diagnosis. EEG abnormalities are present in all epileptic patients in the temporal-occipital regions with the same characteristics, so we could hypothesize that these abnormalities could represent a recognizable EEG pattern of XGS. Behavioral disorders represent an important problem, and longitudinal evaluations are needed to improve the classification of the psychopathological spectrum in XGS.

Giulia Cinelli and Stefania Della Vecchia contributed equally as first authors to this work.
Roberta Battini and Lorenzo Iughetti contributed equally as coordinator/last authors to this work.

1 | Introduction

Xia-Gibbs syndrome (XGS: OMIM #615829) is a genetic disorder characterized by neurodevelopmental disorders, motor incoordination and hypotonia, seizures, sleep apnea and sometime orthopedic, described for the first time by Xia and Gibbs in 2014 (Xia et al. 2014; Yang et al. 2015; Chander et al. 2021).

XGS is caused by variants in the AT- Hook DNA Binding Motif Containing 1 (AHDC1) gene, located on chromosome 1p36.11. The structural organization includes different untranslated exons upstream of a single common 4929 bp coding exon followed by a single downstream untranslated exon AHDC1 has two AT-hook DNA-binding motifs that are typically involved in binding to the minor groove of AT-rich DNA sequences, suggesting a role in chromatin architecture and transcriptional regulation (Xia et al. 2014). The AHDC1 gene can produce different transcript isoforms, all sharing the single coding exon. The variability of the noncoding exons at the 5′ UTR across different isoforms suggests the existence of alternative promoters and splicing events. It also interacts with nuclear proteins and is implicated in axonogenesis (Chatr-Aryamontri et al. 2017; Van Damme et al. 2011; Uhlén et al. 2015). AHDC1 is widely expressed across all sampled tissues and cell lines, with significant variation in expression levels, suggesting tissue-specific regulation and induction. The highest expression is observed in the cerebellum, followed by notable levels in the uterus, skin, and esophagus (García-Acero and Acosta 2017). This broad expression pattern might be associated with the phenotypic spectrum seen in AHDC1 mutations. This condition is today diagnosed through trio whole-exome sequencing (Xia et al. 2014; Yang et al. 2015, 2019; Jiang et al. 2018; Ritter et al. 2018; Cheng et al. 2019; Díaz-Ordoñez et al. 2019; Murdock et al. 2019; Cardoso-Dos-Santos et al. 2020; Gumus 2020). The Xia–Gibbs Society currently documents approximately 530 diagnosed individuals worldwide, while around 97 cases have been reported in the literature, including frameshift, nonsense and missense variants, but excluding microdeletions and microduplications involving AHDC1 (He et al. 2020). In recent years, the clinical and neuroradiological phenotype of the syndrome is being delineated.

It is estimated that about 30% of XGS patients have epilepsy and that 50% have electroencephalogram (EEG) abnormalities (Ritter et al. 2018). Furthermore, behavioral problems complicated the picture, ranging from neurodevelopmental disorders like autism and Attention-Deficit/Hyperactivity Disorder (ADHD) to anxiety, poor impulse control, and self-harm (Xia et al. 2014; Yang et al. 2015). About 60% of XGS patients present brain MRI anomalies, like corpus callosum hypoplasia or dysgenesis, delayed myelination or hypomyelination, leukomalacia, dysmorphic sulci-gyri, and cystic lesions (Xia et al. 2014; Yang et al. 2015; Jiang et al. 2018; Ritter et al. 2018; Cheng et al. 2019; Sennes et al. 2025). However, there are no systematic studies on the epileptological, behavioral and neuroradiological characterization of XGS.

This multicenter cross-sectional study describes the largest Italian cohort of XGS patients and aims to further define the clinical and neuroradiological phenotype of the condition. Moreover, by analyzing brain imaging, EEG recordings and clinical data, we aim to define whether there is a specific neuroradiological and EEG pattern and to characterize the types of seizures present in XGS, guiding the clinician in early diagnosis. Using standardized questionnaires, we aim to outline the neuropsychiatric profile of the Italian cohort of XGS patients in order to better understand their care needs over time. Finally, we try to outline the multidisciplinary evaluations these patients should undergo over time to provide the best possible care and try to prevent certain complications early on.

2 | Material and Methods

2.1 | Study Approval and Patient Consents

This multicentric cross-sectional study was approved by the Modena Pediatric Ethics Committee (610/2021/OSS/AOUMO) and Tuscany Regional Pediatric Ethics Committee (153/2022). All the procedures complied with the Helsinki Declaration of 1975. Genetic studies were performed with written informed consent. All participants (including parents or legal guardians in case of minor patients) received pre- and post-test genetic counseling as per routine practice in the neurogenetics clinics of the participating centers.

2.2 | Patient Cohort

Affected individuals harboring variants in AHDC1 were recruited from collaborating Italian centers coordinated by the University Hospital of Modena (Pediatric Unit) and IRCCS Stella Maris Foundation in Pisa. We enrolled 15 patients with XGS, identified through exome sequencing. Clinical charts were reviewed for information on family history, age at disease onset, age at last examination, and most predominant signs and symptoms.

2.3 | Literature Review

We performed a systematic search on the PubMed database (last access 30 December 2022, 5:00 p.m. CET) from 2014 to 2022. PRISMA Flow Diagram (Della Vecchia et al. 2021) of the review process is presented in Figure 1. The search with "Xia Gibbs syndrome" or "AHDC1" as keywords provided a total of 73 records. After removing duplicates, 48 articles remained for screening. After screening the abstracts, 26 articles were removed because they were literature reviews (6), letters to editors (4), clearly not related to our topic (15), or were written in Chinese (1). After full text screening, further articles were removed because they did not contain sufficient data about the patient's clinical phenotype (2). Studies were included if they met the following criteria: articles had to be written in English and (i) focus on the clinical phenotype and/or (ii) describe the neuroradiological phenotype of XGS. No restrictions were imposed in terms of participants' age or gender. Studies were excluded if they: (i) did not focus on XGS; (ii) were written in languages other than English and Italian; (iii)

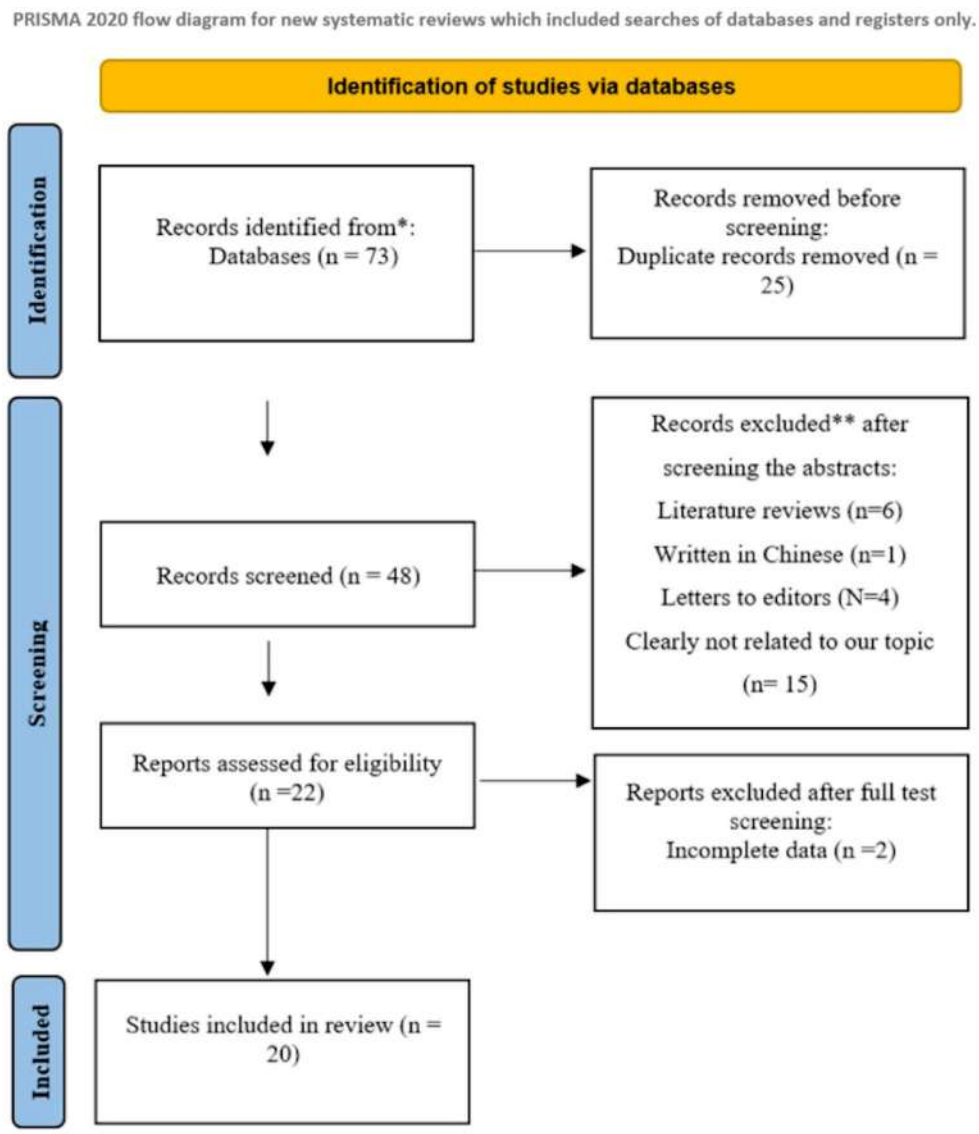

FIGURE 1 | Prisma flow chart.

were letters to editors or reviews. The articles were assessed for eligibility by two authors working independently (GC and SDV), and studies were included only if all three deemed them eligible. Any uncertainty about eligibility was resolved through discussion.

Methods related to EEG recordings, neuroimaging, neuropsychiatric evaluation and statistical analysis can be found in Supporting Information.

3 | Results

3.1 | Genetic and General Features of Our Cohort

Our cohort is composed by 15 XGS patients, 8 females and 7 males, ranging from 1.5 to 17 years of age (median age 11 years) (Table 1). 14/15 patients carry de novo frameshift or nonsense AHDC1 variants. Only one patient presented a missense variant. Nonsense/frameshift variants are distributed across the entire gene. Eight of the intragenic variants are novel, while all others have been reported before in literature or databases (HGMD, Clinvar) (Romano et al. 2022; Khayat, Hu, et al. 2021; Bochicchio et al. 2025; Salvati et al. 2022; Lord et al. 2012). Figure 2 represents pathogenic variants along the AHDC1 gene.

3.2 | Clinical Features

Facial features consistently reveal dysmorphic features; the most common are oval face, anteverted nares, thin upper lip, low set ears, concave nasal bridge, and bulbous nose. However, facial features have to be considered as "nonspecific," and a recognizable craniofacial profile is not available, nor is there a typical gestalt.

Neurodevelopmental disorders are the most frequent clinical features, with intellectual disability present in 86.67% of cases. Motor manifestations are also well represented, with hypotonia and motor incoordination being the predominant ones, followed by ataxia and spasticity. Epilepsy is present in

TABLE 1 | Genetic characteristics of our cohort.

	Nucleotide change NM_001029882.3	Protein change NP_001025053.1	Inheritance	Variant	Age	Gender	ACMG criteria	Phenotype
P1	c.514dup	p. Ser172LysfsTer8	dn	Frameshift	9 years	F	Likely pathogenic (Della Vecchia et al. 2021) (PVS1, PM2)	Epilepsy, language and motor delay, autism, sleep apnea, strabismus, GH deficiency
P2	c.787del	p.Ala263ProfsTer26	DnDndn	Frameshift	16 years	F	Likely pathogenic This paper (PVS1, PM2)	Language and motor delay, autism, sleep apnea, gastroesophageal reflux, strabismus, craniostenosis, congenital dysplasia of the hip, foot deformities
P3	c.1446del	p.Val483TyrfsTer16	DnDn	Frameshift	14 years	M	Pathogenic Clinvar (PVS1, PM2, PP4)	Epilepsy, language and motor delay, autism, sleep apnea, gastroesophageal reflux, strabismus
P4	c.2188G>T	p.Glu730Ter	Dn	Nonsense	15 years	M	Pathogenic (Bochicchio et al. 2025; Khayat, Hu, et al. 2021) (PVS1, PP5, PM2)	Language and motor delay, autism, foot deformities
P5	c.3025C>G	p.Pro1009Ala	Dn	Missense	11 years	F	Likely pathogenic, clinvar (PS4, PM2)	Epilepsy, language and motor delay, sleep apnea, gastroesophageal reflux, strabismus, foot deformities
P6	c.1758dup	p.Arg587ThrfsTer56	Dn	Frameshift	7 years	F	Pathogenic, clinvar (PVS1, PP5, PM2)	Language and motor delay, gastroesophageal reflux, strabismus
P7	c.2468C>G	p.Ser823Ter	Dn	Nonsense	5 years	F	Likely pathogenic (Khayat, Li, et al. 2021) (PVS1, PM2)	Language and motor delay, sleep apnea, strabismus, scoliosis
P8	c.2734C>T	p.Gln912Ter	Dn	Nonsense	2 years	F	Likely pathogenic This paper (PVS1, PM2)	Epilepsy, language and motor delay, gastroesophageal reflux, strabismus
P9	c.3130del	p.Ala1044ProfsTer98	Dn	Frameshift	16 years	M	Likely pathogenic This paper (PVS1, PM2)	Epilepsy, language and motor delay, strabismus, craniostenosis, foot deformities

(Continues)

TABLE 1 | (Continued)

	Nucleotide change NM_001029882.3	Protein change NP_001025053.1	Inheritance	Variant	Age	Gender	ACMG criteria	Phenotype
P10	c.1102_1114del	p.Cys368AlafsTer80	Dn	Frameshift	11 years	M	Likely pathogenic (Romano et al. 2022) (PVS1, PM2)	Language and motor delay, autism, strabismus, foot deformities
P11	c.2588_2589 del	p.Glu863ValfsTer27	Dn	Frameshift	4 years	M	Likely pathogenic This paper (PVS1, PM2)	Language and motor delay, foot deformities
P12	c.2192dup	p.Asp732ArgfsTer36	Dn	Frameshift	10 years	M	Likely pathogenic This paper (PVS1, PM2)	Language and motor delay, autism, strabismus, foot deformities
P13	c.1678A>T	p.Lys560Ter	Dn	Nonsense	9 years	M	Likely pathogenic This paper (PVS1, PM2)	Language and motor delay, autism, sleep apnea, gastroesophageal reflux, strabismus, foot deformities, scoliosis
P14	c.1975delC	p.Leu659CysfsTer73	Dn	Frameshift	11 years	F	Likely pathogenic (Díaz-Ordoñez et al. 2019) (PVS1, PM2)	Epilepsy, language and motor delay, autism, strabismus, foot deformities, scoliosis
P15	c.1975delC	p.Leu659CysfsTer73	Dn	Frameshift	11y	F	Likely pathogenic (Díaz-Ordoñez et al. 2019) (PVS1, PM2)	Epilepsy, language and motor delay, autism, strabismus, congenital dysplasia of the hip, foot deformities, scoliosis

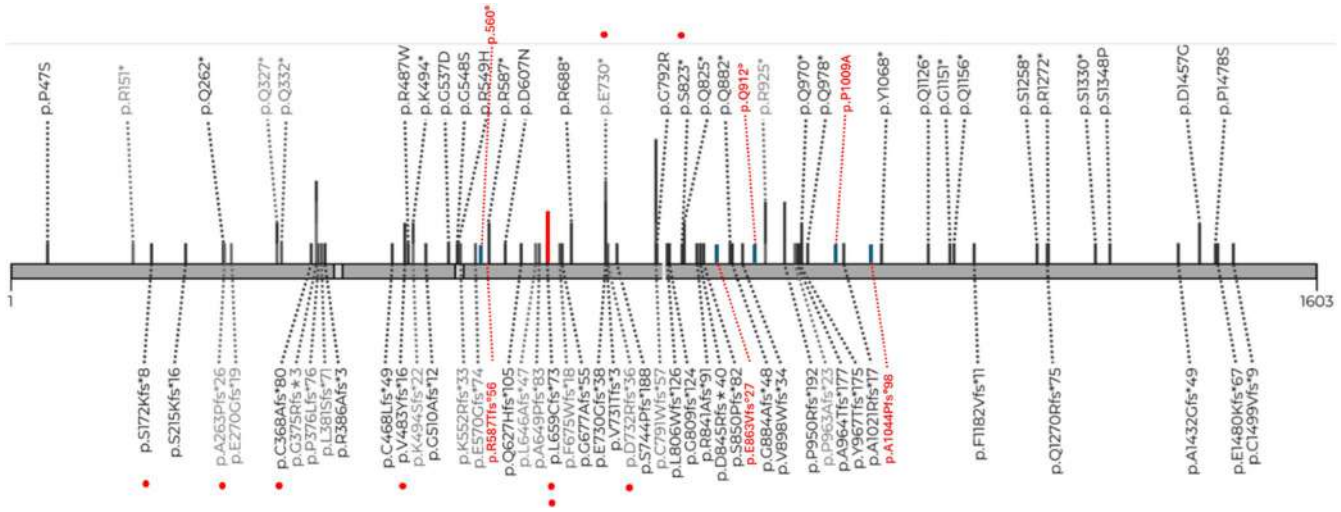

FIGURE 2 | Graphical representation of the AHDC1 gene: In red we have represented the novel variants described in the article.

46.67% of cases and 60% of patients have a positive history of seizures. The most frequent ocular anomaly is strabismus (86.67%), followed by hypermetropia (4/15, 26.66%), astigmatism (3/15, 20%), myopia (2/15%) and nystagmus (1/15, 6.6%). Orthopedic manifestations were also very frequent, especially foot deformity. Endocrine abnormalities were uncommon in our cohort, with hypothyroidism presented in 13.3% of cases (2/15) and GH deficiency in only one patient treated with growth hormone therapy. Gastrointestinal problems were also frequent in our cohort, particularly feeding difficulties within the first month of age in 40% of patients (6/15) and gastro-esophageal reflux in 33.33% (5/15) (Figure 3).

3.3 | Epilepsy and EEG

Clinical history of seizures was mentioned in 7/15 patients (46.67%). Age at the onset of epilepsy was between 2 and 9 years (mean age 5.5 ± 3.02 years); 2 of the 7 epileptic patients had already presented febrile seizures at 1 and 2 years of age, respectively. Semeiology of seizures at onset of epilepsy included focal motor seizures in 3 patients, focal motor seizures with secondary generalization in 2 patients, and generalized seizure in other 2 patients.

Regarding the EEG features of our patients (Tables S1 and S2), structure was quite normal in all patients during the first years of life, while posterior slow activity was observed in 5 patients without epilepsy and in 2 patients before the epilepsy onset. During the follow up, we then observed the onset of focal occipital or temporo-occipital paroxysmal activity, activated during sleep, with a normal background activity. The interictal EEG showed high amplitude spike-polyspike waves and slow waves that were quite common in all the epileptic patients (Figure S1).

Clinical presentations of seizures fluctuated between generalized seizures and both generalized with focal onset seizures (Table S1). Treatment in patients with epilepsy was different; three patients were seizure-free with monotherapy: two were treated with carbamazepine, one with sodium valproate. Four of the epileptic patients presented refractory seizures despite multiple drug combinations. Better outcome was evident in patients with isolated generalized seizures. One patient (n. 5) started carbamazepine with partial response and consequently clobazam was associated without significant positive effect. Association of brivaracetam and carbamazepine helped to achieve better control. At 14 years old, the patient presented focal seizures and secondary generalization. Multiple combinations of antiepileptic drugs were administered, although during the last control he was seizure-free due to valproate and zonisamide. Two of the drug-resistant patients presented brain electric activity mimicking Lennox–Gastaut syndrome with tonic, atonic and tonic–clonic seizures and their EEG pattern was reported previously (Della Vecchia et al. 2021). At seizure onset, these two patients () displayed spike-and-wave bursts mainly over the left parieto-temporo-occipital region on normal awake background activity, diffuse spike/polyspike-slow wave complexes, and generalized paroxysmal fast activity in sleep. During the long-term follow-up, reduced epileptic discharges in wake were found, although still abundant generalized paroxysmal fast activity intermixed with diffuse spike-slow wave discharges during sleep. Patients 6 and 7 showed different epilepsy evolution. Patient 6 started therapy with lamotrigine with no effect even in combination with valproate. Consequently, multiple combinations of antiepileptic drugs were administered: despite therapy with levetiracetam, valproate, ethosuximide, and nitrazepam, the girl still presents multiple episodes of seizures. Patient 7 was treated with valproate and lamotrigine with complete remission. The combinations of epilepsy manifestation and antiepileptic drugs were summarized in Table S3.

The EEG recorded of patients who did not develop epilepsy showed abnormalities in five cases, with slow electric activity mainly in posterior regions in 4 of them (Table S2).

Figure S2 shows the EEG of two of the non-epileptic patients: the first showed spike complex and slow spike–waves in the posterior regions, while the second had a slow spike–wave complex in the left frontal regions and presented major behavioral issues. The posterior EEG abnormalities detected during the first years of life may represent a typical characteristic EEG sign of the syndrome.

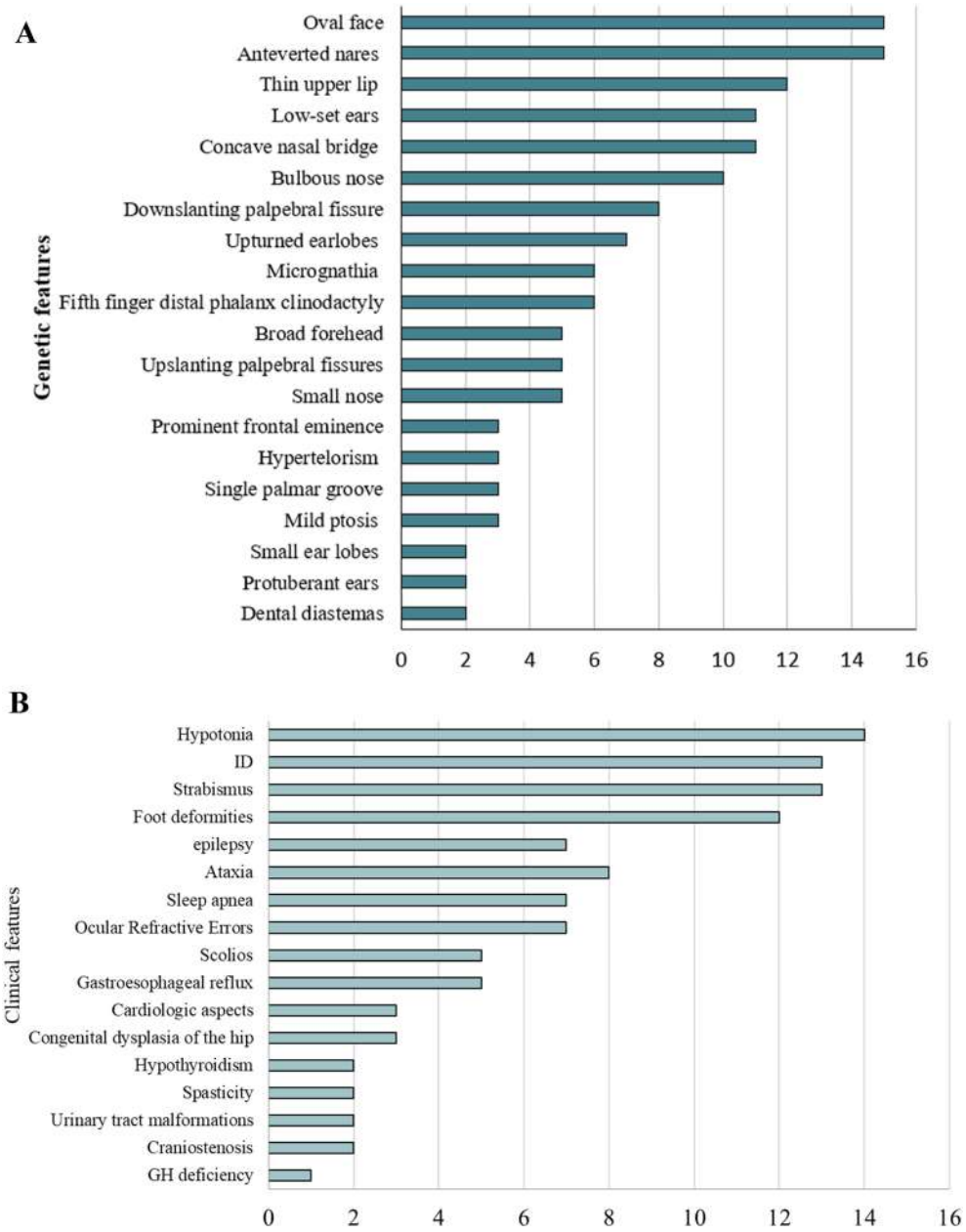

FIGURE 3 | (A) Clinical manifestations of our XGS cohort. (B) Dysmorphological features of our XGS cohort.

3.4 | Psychopathological Profile

The psychopathological assessment revealed the presence of several neurodevelopmental, behavioral and affective problems in our cohort. Social communication questionnaire (SCQ) was performed on 14/15 patients in order to screen the risk of ASD. Considering a TN positive plus SCQ≥15, 8/14 patients (~60%) were at high risk of ASD, without differences in SCQ scores between males and females (F = 4, M = 4). Adding also the potential false negatives with a scoring of 11–14 points ($n = 3$ with a SCQ score of 14), 11/14 (78.5%) patients presented ASD features (F = 5, M = 6). Among them, only four were evaluated using Autism Diagnostic Observation Schedule (ADOS)-2, a standardized semi-structured observational assessment of the child (Tager-Flusberg et al. 2009), confirming the diagnosis of ASD. Figure S3 shows SCQ results. We found no differences in SCQ scores between the epileptic and non-epileptic (NE) group (Table S4). To determine the impact of age and language level on the SCQ score a multi-linear regression was conducted with total SCQ score as the dependent variable. When age and language level were entered as covariates, we obtained a significant model of the SCQ score ($R^2 = 0.57$, $F = 9.69$, $p = 0.04$). In this model age ($\beta = 1.34$, $p = 0.0011$) had independent contribution while language level ($\beta = 1.72$, $p = 0.162$) had no independent contribution.

Child Behavior Checklist (CBCL) questionnaire assessing psychopathological profile was performed on 14/15 patients, 4 patients were evaluated with CBCL $1^{1/2}$–5 years and 10 patients with CBCL 6–18 years. Table 2 shows CBCL scores. In preschool age, we observed a prevalence of internalizing problems, with borderline scores for withdrawn (median T score = 67) and pervasive developmental problems (median T score = 65.5) and clinical scores for attention problems (median T score = 71.5). On the contrary, with

TABLE 2 | CBCL scores.

CBCL 1½–5 years	Median	IQR	CBCL 6–18 years	Median	IQR
Internalizing	59	2.75	Internalizing	57.5	6.25
Externalizing	55	2.75	Externalizing	**67.5**[b]	5.5
Total problems	59.5	5.25	Total problems	**70.5**[b]	6
Syndrome scales					
Emotionally reactive	55	8.25	Anxious/depressed	54	5
Anxious/depressed	54	4	Withdrawn/depressed	60	4.75
Somatic complaints	54	9	Somatic complaints	55.5	13.25
Withdrawn	**67**[a]	2.75	Social problem	**71**[b]	11
Sleep problems	57.5	5.75	Thought problems	**73**[b]	6.5
Attention problems	**71.5**[b]	7.75	Attention problems	**73.5**[b]	11.75
Aggressive behavior	51	0.5	Rule-breaking behavior	64.5	7
			Aggressive behavior	**70.5**[b]	8.5
DSM-oriented scales					
Affective problems	58	8.75	Affective problems	**65.5**[a]	5.75
Anxiety problems	58.5	10.75	Anxiety problems	63	9.5
Pervasive development problems	**65.5**[a]	7.25	Somatic problems	50	5.5
ADHD	57	1.5	ADHD	**70**[b]	5.5
Oppositional defiant problems	50	0.5	Oppositional defiant problems	64.5	12.25
			Conduct problems	63.5	8.5
			Sluggish cognitive time	**68**[a]	9.5
			OCD	63	14
			PTSD	64	3.5

Note: The Bold font refers to values characterized by the presence of a superscript letter ("a" or "b").
Abbreviations: ADHD, attention deficit hyperactivity disorder; IQR, range interquartile; OCD, obsessive compulsive disorder; PTSD, post traumatic stress disorder.
[a]Borderline score.
[b]Clinical range.

growth, there is a prevalence of externalizing problems (median T score = 67.5). In particular, we observed clinical scores for aggressive behavior (5/10), social problems (6/10), thought problems (7/10), attention problems (6/10), and ADHD scale (5/10), and borderline scores for affective disorders (3/10).

Then we investigated any possible differences in CBCL scores between the epileptic and NE groups, considering only CBCL 6–18 years, because we have only four patients in the preschool age (two with and two without epilepsy). Considering CBCL 6–18 years, indeed, there are five patients with epilepsy and five patients without epilepsy. Comparing the epileptic (E) and NE group, we observed no differences between the two groups in all CBCL scales (summary, syndrome, DSM-oriented scales) as shown in non-parametric statistics in the Tables S5 and S6. Figure S4 summarized clinical scores of CBCL in the epileptic group, NE group and total group. There are no differences in summary scales; all patients presented clinically significant scores in externalizing and total problems. In the syndrome scales, the epileptic group presented clinically significant results in social problems and aggressive behavior more frequently than NE patients, but this result was not statistically significant. In DSM scales, ADHD score was clinically significant in 5/10 patients, but no differences between the epileptic and NE groups were found.

We also investigated a correlation between the age of the patients and CBCL scores, finding a positive correlation between the age of the patients and the scores of the social problems (rho = 0.72, $p = 0.028$) and attention problems (rho = 0.768, $p = 0.021$).

3.5 | Language Function, Cognitive Profile and Adaptive Skills

We used levels of expressive speech described in Tager-Flusberg and colleagues' work to define spoken language of our cohort ranging between 1 and 17 years-old (Khayat, Li, et al. 2021), finding that 12/15 patients (80%) had a spoken language constituted by preverbal communication, single word, or combination of two words. The details of spoken language are reported in Figure S5A. The evaluation of intellectual disability using standardized scales in our cohort is extremely heterogeneous,

because different diagnostic tests were used. Most of the patients were evaluated with non-verbal Leiter scale or Peabody scale. WISCV IV was performed in two patients, WPPSI-III in two patients and WISCIII in one patient. To better classify intellectual disability in our cohort, we decided to use data from the VABS-2 as a proxy for developmental level. VABS-II was performed to define adaptive skills on 14/15 patients. Most of patients present severe (66.7% of patients) or moderate ID (16.7% of patients). As shown in Figure 5B, VABS-2 scores are below average for all scales. Total-VABS, communication and daily activity skills scores refer to a severe disability, while socialization and motor skills refer to a moderate disability. We found no differences in VABS scores between the epileptic and NE group (Table S7). We then analyzed whether there was a correlation between adaptive functioning and age in our cohort, finding a negative correlation between the age and all the subscales and total-VABS score, as shown in Figure S5C.

3.6 | Neuroradiological Features of Our Cohort

All patients underwent brain MRI, while only two patients also underwent spine MRI. Most patients had only one MRI exam, but nine patients had two or more. No patients had normal brain MRI, and one of these had an altered spinal MRI. The observed features and their frequency are summarized in Table 3. Figure S6 shows neuroradiological findings of some patients of our cohort. No correlation between intellectual disability and brain MRI was found ($p=0{,}180$). On the other hand, MRI changes showed moderate correlation with the presence of epilepsy ($p=0.026$).

TABLE 3 | MRI findings in XGS patients.

Neuroradiological findings	Number of patients	%
Posterior fossa malformations	8	53.33%
Mega cisterna magna	7	87.50%
Hypoplasia of the left cerebellar hemisphere	1	12.50%
Cystic lesion	5	33.33%
Arachnoid cyst	4	80.00%
Choroid plexus cyst	1	20.00%
White matter abnormalities	7	46.67%
Periventricular leukomalacia	1	16.67%
Gliosis of the peritrigonal regions	1	16.67%
Delayed myelination or hypomyelination	6	85.71%
Lateral ventricle morphology abnormalities	10	66.67%
Dilation of lateral ventricles	7	70.00%
Temporal horn enlargement	1	10.00%
External hydrocephalus	1	10.00%
Other ventricular dysmorphisms	1	10.00%
Dysmorphic sulci-gyri	1	6.67%
Thin corpus callosum	12	80.00%
Cerebral atrophy	1	6.67%
Partial hippocampus malrotation	4	26.67%
Dilation of Virchow Robin	4	26.67%

4 | Literature Review

We included 20 papers in our review and used the literature data for a comparison with our XGS cohort (Figure 4). We found a higher frequency of sleep apnea, growth and feeding problems, strabismus, and foot deformities. Epilepsy is very frequent in our cohort, but the frequency was not significantly different from literature (46.67% vs. 32.90%). Regarding the neuroradiological phenotype, one of the most common malformations in our cohort was thin corpus callosum (73.3%), followed by posterior fossa malformations (53.33%) and lateral ventricle morphology abnormalities (66%). Partial hippocampus malformation was present in 26.67% of patients. The most frequent malformation in posterior fossa was large cisterna magna (46.67%). All these MRI anomalies are more represented in our cohort than literature data. Delayed myelination and cystic lesions were more frequent compared with literature cohort, but not statistically significant. Other alterations were dysmorphic sulci-gyri, leukomalacia, hypoplasia and external hydrocephalus have the same incidence reported in literature. One patient presented spine MRI alterations with anchored medulla and fibro lipoma of the terminal filum evident from L3-L4 somatic disc and extending to S3.

5 | Discussion

XGS is a newly defined genetic syndrome linked to heterozygous variants in the AHDC1 gene. De novo stop-gain and frameshift mutations in the gene encoding the AHDC1 protein (Gibbin) that are predicted to lead to truncated AHDC1 protein synthesis are well-established as an underlying cause of XGS. The presence of a single coding exon suggests that mutant mRNAs may escape the nonsense-mediated decay (NMD) surveillance mechanism, resulting in the translation of possible truncated forms of the protein, as experimentally confirmed for some AHDC1 mutations by Chander et al. (2021) and suggesting a dominant-negative or a gain-of-function mechanism underlying XGS (Bochicchio et al. 2025). In addition to de novo protein-truncating mutations, at least 10 de novo missense mutations are reported (He et al. 2020; Bochicchio et al. 2025) predicted to result in full-length protein products, providing additional support for the hypothesis of a dominant-negative or gain-of-function pathogenetic mechanism (Jiang et al. 2025).

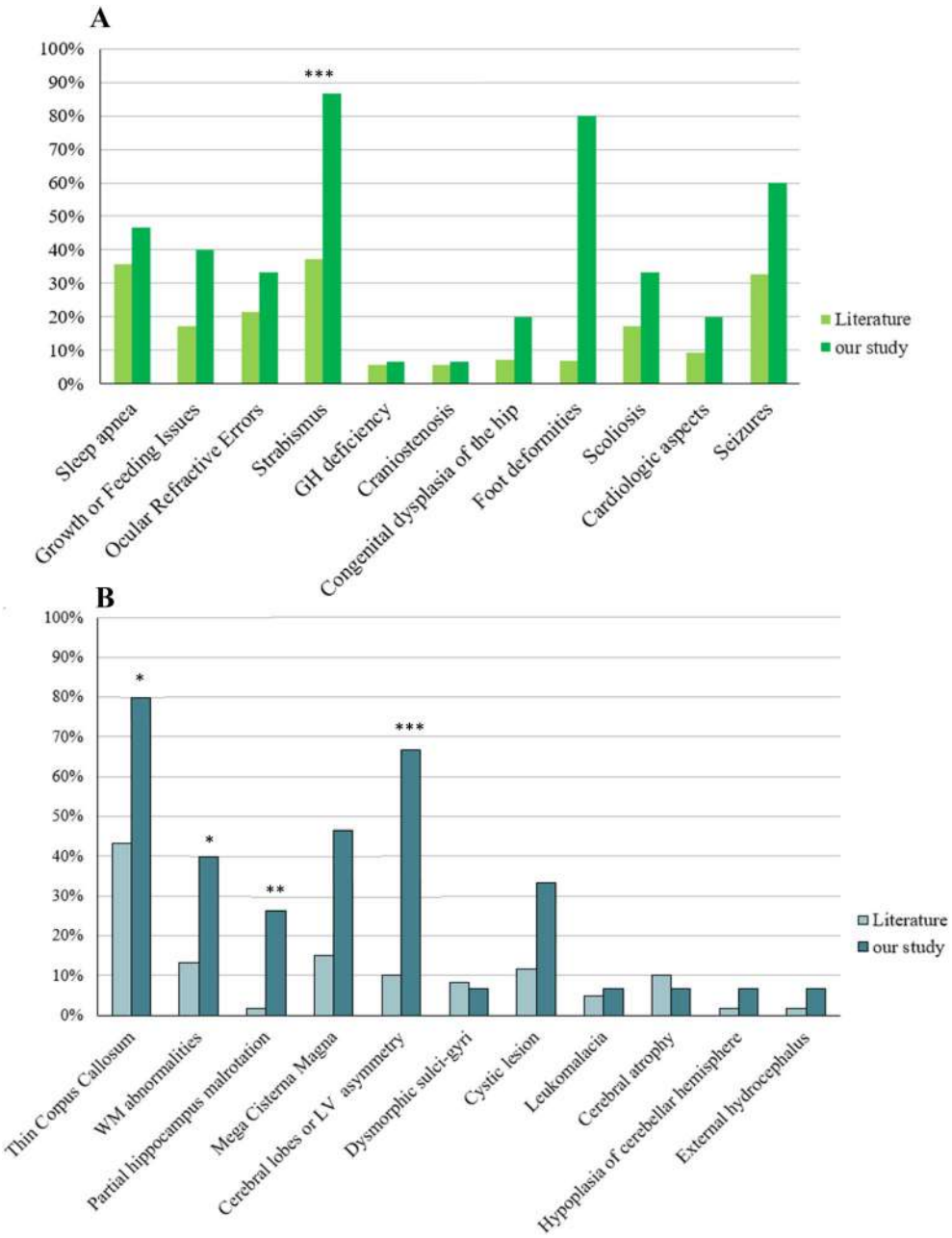

FIGURE 4 | (A) Clinical manifestation findings in our cohort ($n = 15$) compared with brain clinical findings in literature ($n = 70$). (B) Neuroradiological findings in our cohort ($n = 15$) compared with brain MRI findings in literature ($n = 60$). Statistical comparisons of the frequencies of clinical manifestations in our cohort versus literature-reported cases. Asterisks indicate statistical significance: *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

Patients with large de novo deletions encompassing the entire AHDC1 locus and diagnosed with XIGIS-overlapping features (Cheng et al. 2019), have also been reported, suggesting that AHDC1 haploinsufficiency may also be a potential pathogenic mechanism. However, the haploinsufficiency mechanism is controversial due to the other genes deleted, which may contribute to the XGS-like phenotypes and the observation of an RNA mono-allelic expression pattern with no deficiency in its overall expression levels in a XGS patient presenting the smallest known contiguous deletion of AHDC1 (~350 kb) (Chander et al. 2021).

Genotype–phenotype correlations of the variants have also been proposed, A recent work performing latent class analysis (LCA) of 97 published mutations stratified on three distinct phenotypic subtypes (Ataxia, Sleep Apnea & Short Stature, and Neuropsychological) observed no clear correlation between the variant position and the identified subtypes (Goyal et al. 2020). Liberati et al. (2009) provided statistically significant support for previously reported genotype–phenotype associations by Jiang et al. (2025), between pathogenic variants in the first half of the AHDC1 coding region and the occurrence of epilepsy and scoliosis and proposed a novel association between N-terminal variants and developmental regression.

As regards our cohort, only 2 of the variants are not in the C terminus, according to the classification proposed by Khayat,

and only one in 1/3 of the gene, making a genotype–phenotype correlation not possible.

In this study, we described the largest Italian cohort of XGS patients, reporting 4 novel variants: 2 nonsense and 2 frameshifts. Compared to the literature data, our population presented a higher frequency of sleep apnea, growth and feeding problems, strabismus and foot deformities. We also observed a high frequency of epilepsy in our cohort, similar to the work of Chander et al. (2021), in which half of the affected individuals had seizures. Clinical manifestations of seizures were heterogeneous, including tonic–clonic seizures, focal with secondary generalization seizure, atonic seizures, sleep-related seizures and reflex seizures (Xia et al. 2014; Yang et al. 2015; Murdock et al. 2019; Cardoso-Dos-Santos et al. 2020). In focal arising seizure a common pattern including staring eyes and impaired awareness with subsequent generalization was observed in 4 patients. The age at onset of seizures was variable and, in our study, ranged from 2 to 9 years, with a median age of 5.4 years. Interestingly, we found a reproducible EEG pattern in pre-scholar age characterized by normal background activity and paroxysmal abnormalities localized mainly in the posterior regions, characterized by high voltage spike-slow waves, worsened by sleep. This type of pattern EEG was revealed in some patients before the clinical manifestation of epilepsy and could be a potential risk factor for developing seizures. To date, no studies have systematically characterized the EEG features of patients with Xia–Gibbs Syndrome, making our findings an important preliminary step toward defining its distinctive electroencephalographic profile. Regarding treatment, seizure remission following antiepileptic therapy was highly variable, reflecting a heterogeneous response to pharmacological management, but we observe a potential early response to NA-channel inhibitor in most of patients. As previously reported in the literature (Lord et al. 2012), epilepsy in XGS can also be drug-resistant and may mimic the electroclinical features of Lennox–Gastaut syndrome.

Several psychiatric issues have been described in patients with XGS, including ASD (Romano et al. 2022), aggressive behavior or self-injurious behavior (Yang et al. 2019; Lord et al. 2012; Jiang et al. 2025), anxiety disorders (Ritter et al. 2018; Díaz-Ordoñez et al. 2019), obsessive-compulsive disorder (Ritter et al. 2018), impulse control difficulties (Yang et al. 2019) and schizophrenia during adolescence (Cardoso-Dos-Santos et al. 2020). However, this is the first study attempting to investigate psychopathological manifestations consistently by means of questionnaires. Our analysis revealed the presence of internalizing problems and neurodevelopmental disorders such as ID, speech and language disorders, ASD, and ADHD in pre-school age, complicated by externalizing problems, thought problems, and affective disorders during childhood and adolescence. This is in line with what we have previously observed in a girl with XGS followed over time, who started out with ASD and showed worsening psychiatric manifestations with a prevalence of externalizing problems over time (Romano et al. 2022). From ~60 to ~80% of the patients in our cohort, depending on the SCQ cut-off used, were at risk of autism. Ritter et al. (2018) showed that a linear relationship exists between the M-CHAT score for autism, the square root of age, and the language capability ratings. The equation indicates that the M-CHAT score increases with age, but the rate of increasing slows down year by year. We partially confirmed these data, observing an independent impact of age on the SCQ score, but no impact of language level on the SCQ score. Furthermore, we observed no differences between SCQ and CBCL scores between epileptic and NE patients. Although our sample was restricted, we showed a positive correlation between patients' age and the scores of the social and attentive issues. These relevant problems may have benefited from behavioral and emotional interventions. Consultation with a neuropsychiatrist may be helpful in guiding parents through appropriate behavior management strategies or providing prescriptions for medications, such as the medication used to treat ADHD, aggressive behavior, anxiety, and mood problems, when necessary (Chander et al. 2021).

VABS-2 interview revealed that most patients presented an IQ below the 1st percentile in all the scales. We found negative correlations between age and VABS subscales indicating a worsening of adaptive skills over time. Moreover, no differences in VABS scores between the epileptic and NE group were seen in our XGS population. Our study thus suggests that epilepsy does not have any impact on the behavioral profile and adaptive skills, but that psychopathological and cognitive features observed in XGS patients can be ascribed to gene mutation.

Identifying orthopedic problems is crucial for setting up a targeted physiotherapy plan. Goyal et al. (2020) described an example of early physiotherapeutic intervention in a patient with XGS based on the principles of neurodevelopmental treatment (NDT) and sensory integration (SI).

Specific feeding problems in XGS may include sucking and swallowing difficulties, recurrent vomiting, and gastroesophageal reflux disease. In this study, 40% of our patients presented with oral hypotonia and gastroesophageal reflux, but only one patient needed gastric tube placement. In the literature, few studies were reported to evaluate aspiration risk and nutritional status (Yang et al. 2015; Jiang et al. 2018; Ritter et al. 2018; Gumus 2020). Sometimes, feeding difficulties can determine an impaired linear growth: most of these patients have a normal birth weight but develop poor postnatal growth due to feeding problems related to both hypotonia and the behavioral aspects of the syndrome (Chander et al. 2021).

A variety of cerebral anomalies have been reported before in XGS patients, but this is the first study in which a large cohort has been described systematically through a careful analysis of diagnostic imaging data. Despite the limitations of a retrospective design, it allowed us to delineate the frequency of the neuroradiological findings. The most frequent brain MRI alteration was the thin corpus callosum, followed by the posterior fossa malformations and the lateral ventricle morphology abnormalities. The higher frequency of brain MRI abnormalities in our cohort could depend on methodological issues such as different MRI protocols and diagnostic criteria, as well as on the evaluation performed by clinical experts on rare diseases. Almost all the features were stable and did not involve myelination defects or atrophies deserving a longitudinal evaluation. One patient presented spine MRI alterations with anchored medulla and fibro lipoma of the terminal filum evident from L3-L4 somatic disc and extending to S3. No alterations in spine MRI were previously reported in literature. Genotype–phenotype correlations

remain uncertain. Khayat et al. hypothesized that truncating pathogenic variants affecting residue closer to the N-terminal may determine a milder clinical phenotype with better cognitive performances (Jiang et al. 2025). This hypothesis was supported by the observation that patients bearing variants closer to the C-terminus of the protein are nonverbal and have a higher risk of autism (Chander et al. 2021; Ritter et al. 2018; Gumus 2020). On the other hand, truncating pathogenic variants near the N-terminus of the protein have been associated with a statistically significant higher risk of developing seizures and scoliosis (Jiang et al. 2025). In our cohort, we cannot infer genotype–phenotype correlations.

The main limitations of this study are related to its retrospective and multicenter design that partially impaired the homogeneous and systematic collection of the data. The follow-up was performed with different protocols and timing and a variety of assessment tools. However, sharing the outcome study protocol will fill the lack of prospective data for future studies to accurately describe the clinical course and natural history of the disease.

6 | Conclusions

In this study, we report the largest Italian cohort of patients with XGS, an ultrarare genetic disorder. Epilepsy and brain anomalies emerged as frequent and clinically relevant features. Although MRI findings are often non-specific, their association with other clinical characteristics of the syndrome may support clinicians in achieving an early and accurate diagnosis. In all epileptic patients, EEG abnormalities were consistent and localized in the temporal–occipital regions, suggesting the presence of a potentially recognizable electroencephalographic pattern distinctive of XGS. Importantly, this work provides the first systematic psychopathological analysis in XGS, offering a structured evaluation of behavioral and emotional functioning. Our findings underscore that behavioral disturbances represent a major and evolving component of the clinical phenotype, reinforcing the need for longitudinal assessments to better delineate the developmental trajectory and refine the classification of behavioral and affective profiles. Orthoptic and orthopedic problems, even when clinically silent, also warrant careful and ongoing monitoring to ensure timely intervention. Overall, the management of XGS patients requires a multidisciplinary and highly specialized approach, with structured follow-up protocols aimed at preventing complications and promoting early supportive therapies to optimize long-term outcomes. However, given the small sample size and the inherent phenotypic variability of the syndrome, our findings should be regarded as preliminary and descriptive, providing a valuable foundation for future multicentric longitudinal studies.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.