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ORIGINAL ARTICLE

Kohlschütter–Tönz syndrome: clinical and genetic insight on patients with ROGDI variant

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ABSTRACT

Background: Kohlschütter–Tönz syndrome (KTS) is a rare genetically heterogeneous autosomal recessive syndrome initially described in 1974 and characterized by the triad of infantile-onset epilepsy, amelogenesis imperfecta, and developmental delay. KTS patients share a common genetic trait, namely a variant in the *ROGDI* gene, a gene of unknown function that maps to chromosome 16p13.3.

Methods: Following appropriate ethical and logistical measures, we reviewed literature cases with the *ROGDI* variant and presented one novel case diagnosed using whole exome sequencing. Clinical, genetic, developmental, and radiological data were reviewed and compared accordingly.

Results: There were 22 studies involving the *ROGDI* variant, including one additional novel case we reported. Thirteen patients were males, and ten were females. The current age range was 2–24 years. The majority of patients had their first seizure episode between 6 and 12 months. Birth parameters were within normal limits. The majority had unspecified forms of seizures, followed by generalized tonic-clonic and focal tonic-clonic seizures with secondary generalization. Patients with controlled seizures were likely on levetiracetam. Amelogenesis imperfecta and yellowish teeth were distinctive hallmarks. Behavioral problems were observed in one-third of the cases. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) were abnormal in nearly one-third of the cases.

Conclusion: Identifying and drawing conclusive evidence for patients with the *ROGDI* variant was challenging. Conflicting reports on the efficacy of different anti-seizure medications and the adequate treatment modalities were observed. Potential hallmarks continue to be established. Current evidence can be validated, and a delineation of clinical and molecular findings can be achieved with additional cases.

Keywords: Kohlschutter–Tonz syndrome, epilepsy, amelogenesis imperfecta, *ROGDI*, pediatric.

Introduction

Kohlschütter–Tönz syndrome (KTS) is a rare genetically heterogeneous autosomal recessive syndrome characterized by the triad of infantile-onset epilepsy, amelogenesis imperfecta, and developmental delay (1,2). KTS was initially described in 1974 by Kohlschütter, Tönz, and colleagues in a Swiss nonconsanguineous family (3). The syndrome is characterized by its ultra-rare prevalence of <1/1,000,000 (4). Furthermore, it manifests with three distinguishable pillars (Figure 1). The first pillar includes infantile-onset epilepsy which is often refractory to treatment (5). The second pillar includes enamel defects that can be clinically recognized. Moreover, phenotypic variability was reported in the third pillar, which is developmental delay (5–8). Even within the families, the clinical course and the severity of the disease are variable. KTS has no recognized biochemical or other diagnostic indicators. Moreover, it has recently been established that mutations in the *ROGDI* gene are the etiology of the condition, however, only three families' assets of molecular data have been

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reported (7). Evidence illustrated a common genetic trait in patients with KTS, namely, the *ROGDI* gene, a gene of unknown function, which maps to chromosome 16p13.3 (7–9). However, other reports described individuals with *ROGDI*-negative KTS carrying biallelic *SLC13A5* mutations (10). So far only the two genes were associated with KTS. Differences in phenotype, seizure semiology, and clinical events are noted among patients with variants in the *ROGDI* and *SLC13A5* genes (11). Despite that, both mutations cause KTS and *ROGDI*-associated variants rarely present during neonatal periods (10). Nonetheless, in this study, we present a novel case of a patient carrying a homozygous *ROGDI* gene mutation. Furthermore, due to the natural course of this syndrome and the recent advancement in genetic analysis techniques, only a very limited number of cases with KTS have been reported in the literature. To the best of our knowledge, this is the first reported case in Saudi Arabia.

Subjects and methods

The study obtained ethical approval from the Unit of Biomedical Ethics Research Committee at the Faculty of Medicine, King Abdulaziz University (Reference No. 265-23). The study was conducted under the guiding principles of the World Medical Association Declaration of Helsinki. Patients personal data were masked and consent was obtained before the enrollment of the local cases. All information was kept private and anonymous.

Following the narrative review checklist developed by Green et al. (12), we searched all available publications on KTS. The search was restricted to case reports that explicitly mentioned a pathogenic *ROGDI* variant. All articles of KTS patients with *SLC13A5* mutations were excluded from the study. Search terms included the following: A) KTS B) *ROGDI*. The search was carried out using MEDLINE/PubMed, Google Scholar, EMBASE, Scopus, Web of Science, EBSCOhost databases. The following data were retrieved: genetic variant, gender, current age, age of seizure onset, birth time (i.e., at term, pre-term, and post-term), birth parameters (i.e., weight, height, and head circumference), history of neonatal asphyxia, any reported pregnancy complications, seizure semiology, used anti-seizure medications (ASMs), response to ASM, teeth abnormalities (i.e., amelogenesis imperfect, yellowish discoloration, and dental carries), and developmental delay (i.e., cognitive, sensorimotor, speech and language, socioemotional, brain abnormalities, eyes abnormalities, head and face deformities, genitourinary

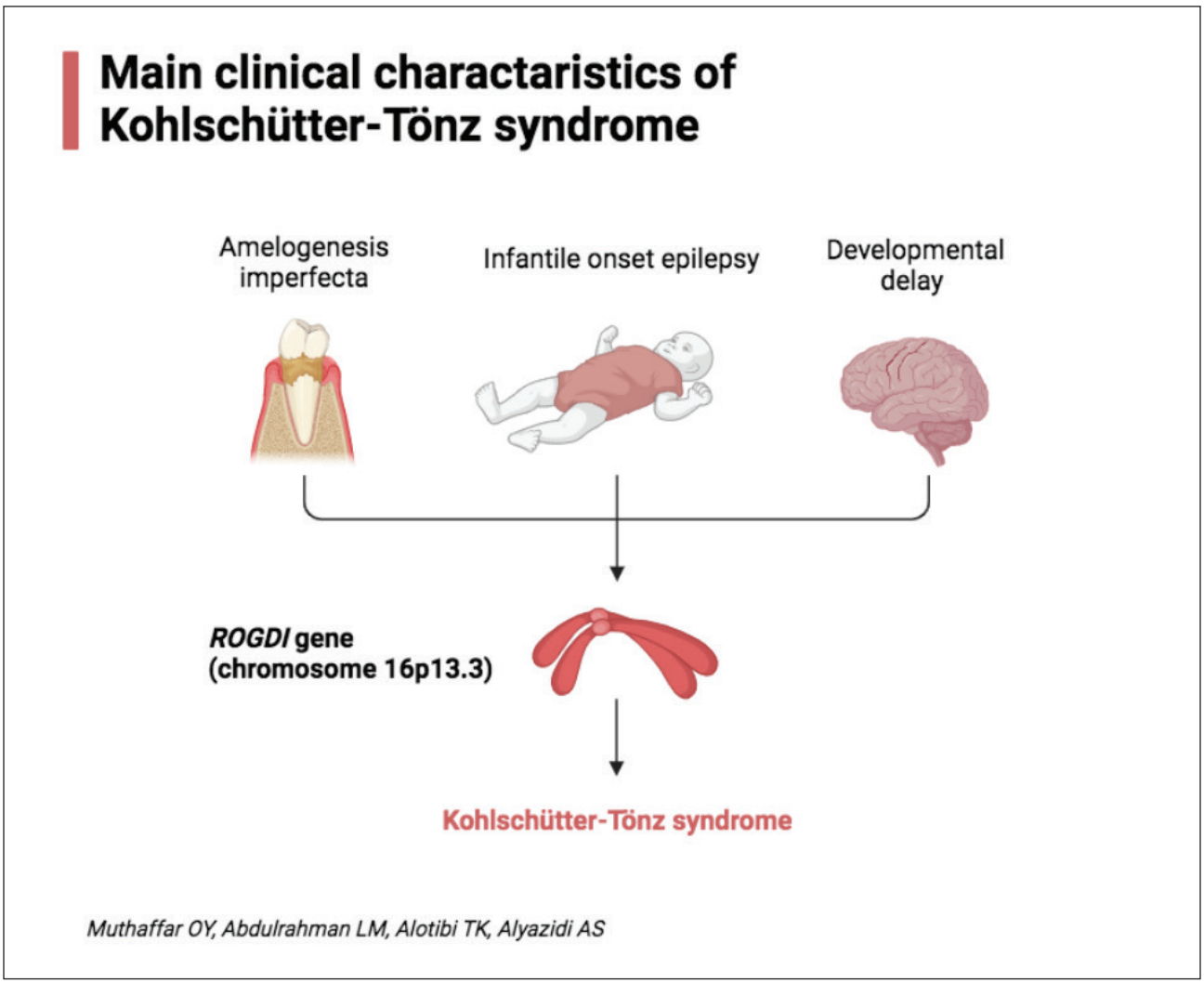

Figure 1. *KTS clinical and genetic hallmarks.*

complications, musculoskeletal abnormalities, recurrent infections, failure to thrive, behavioral problems, and electrographical and neuroradiological data). After synthesizing the obtained cases, only 23 cases, including a novel case, were included in the study. To the best of our knowledge, this study serves as the first comprehensive study to identify, analyze, and compare patients with *ROGDI* variants at this broad scale.

Following appropriate ethical and logistical measures, we obtained the genetic sample of the patients from King Abdulaziz University Hospital. Whole exome sequencing (WES) testing was carried out on the two affected siblings and their respective parents. Sequencing is performed on genomic DNA enriched for the exome using a sequence capture method. Direct sequencing of the amplified captured regions was performed using 2X150bp reads on Illumina next-generation sequencing (NGS) systems. Primary data analysis is performed using Illumina bcl2fastq converter v2.19. Secondary analysis is performed using Illumina DRAGEN Bio-IT Platform v.3.4.12. Tertiary data analysis is performed using SnpEff v5.0 and PerkinElmer's internal ODIN v.1.01 software. Copy number variation and absence of heterozygosity are assessed using BioDiscovery's NxClinical v5.1 software.

Following the CARE Guidelines, we report a case of a Saudi male child currently 12 years old. He presented to our hospital at the age of 9 years with epilepsy, intellectual delay, and speech delay. He had an early onset of seizure at the age of 3 months which was fever provoked. The patient's father is a 43-year-old healthy male and a heterozygous carrier of the *ROGDI* variant. His mother, and the father's wife, is a 35-year-old healthy female. She is also a heterozygous carrier of the *ROGDI* variant. The husband and wife are of positive consanguineous marriage and there is a positive family history of epilepsy. In the patient's first year of life, he was placed on valproic acid and his seizure was subsequently controlled. He had no seizures for two years so the treatment was tapered down and withdrawn. He then had one fever-provoked convulsion and started to manifest with generalized tonic-clonic (GTC) seizure, he was then started on valproic acid. Two years later, he continued to have GTC seizures. No more seizures after levetiracetam was introduced. He was also referred to genetic evaluation and underwent WES testing, the patient revealed that he was compound homozygous for paternally inherited c.117+1G>A chr16:4802381C>T (NM_024589.3) variant in the *ROGDI* gene and maternally inherited c.117+1G>A chr16:4802381C>T (NM_024589.3) variant in the *ROGDI* gene. The c.117+1G>A variant is a substitution of a G with an A one nucleotide after the end of exon 2 of the ROGDI gene. The patient has also been labeled as a Floating-Harbor syndrome patient with uncertain significance heterozygous pathogenic variant at the *SRCAP* gene c.4951C>T (p.Pro1651Ser). The c.4951C>T (p.Pro1651Ser) missense variant results in the substitution of the proline codon at amino acid position 1651 with a serine codon.

Regarding the child's clinical presentation, he had amelogenesis imperfecta in his teeth and continued to have intellectual delay, obeying simple commands, and being unable to tell a story. His developmental age was around 3-4 years. No abnormal findings during the physical examination. As for neuroimaging, magnetic resonance imaging (MRI) of the brain was performed at an external hospital and revealed normal findings. EEG was also performed and revealed possibly a few spikes during sleep. In general, both MRI and EEG were reassuring. Laboratory workup showed normal liver and renal functions. During their clinic visit, we noticed possibly similar signs of his younger sister. She was a 1-year-old female child and was recommended to undergo genetic evaluation due to the strong family history of epilepsy and the presence of a pathogenic variant within the family. WES was performed and revealed a genetic mutation in the same gene as in her family members.

Results

After constructing the methodology, our search yielded 22 studies with *ROGDI* variant including one additional novel case reported by the study authors which was never been described in the literature. Thirteen patients were males and 10 were females. Their current age ranged from 2 to 24 years. The youngest diagnosis of seizure was made upon birth for case number 15 while the latest age was 42 months. The majority of patients were diagnosed between 6 and 12 months (n = 17). The mean current age and mean age of seizure onset were 83 and 7 months, respectively. Of the 22 patients, 2 were pre-term births (9%) while others were full-term babies. Birth parameters were not available to all patients, however, birth weight was within normal limits for the majority of patients (range 2400-3800 g). Neonatal asphyxia and birth complications were not reported among the patients. Detailed baseline data were presented in Table 1.

Regarding patients' seizure patterns, the majority had unspecified forms of seizure followed by GTC, and focal tonic-clonic with secondary generalization. As for current ASMs, levetiracetam, phenobarbital, clobazam, ethosuximide, primidone, phenytoin were all reported. Past medical history included further ASM types. Complete seizure control was achieved among five patients. Of those patients, two unrelated cases were exclusively on levetiracetam. Partial control was observed among cases number 10 and 11. Five patients continued to experience refractory seizures despite administrating multiple ASMs. Case number 3 had 2 seizures per month and was on phenobarbital and levetiracetam. Detailed data on the seizure semiology, used ASMs, and treatment response were illustrated in Table 2.

As for the developmental history, developmental delay was assessed across four domains. The first domain is cognitive delay. All patients, except for two patients who were not mentioned, had a delay in cognitive functions (90.9%). The second domain was sensorimotor in which 16 experienced a delay in this domain (72.7%). Five patients had negative delays in the sensorimotor domain (22.7%). The third domain was speech and language. All patients, except for those who were not mentioned, had a delay in their speech and language. The fourth and last domain was the socioemotional in which only four

Table 1. *Baseline characteristics.*

Case no.	Genetic variant	Sex	Current age	Age of diagnosis (seizure onset)	Birth time	Birth parameters			Neonatal asphyxia	Pregnancy complications
						Weight	Height	HC		
1 (present case)	*ROGDI*	M	11 years	7 years	At term	NM	NM	NM	—	—
2	*ROGDI*	F	2 years	5 months	At term	BW 3450 g 13 kg at admission	89 cm at admission	48 cm at admission	NM	—
3	*ROGDI*	F	2 years	7 months	Preterm	BW 3800 g 13 kg at admission	84 cm at admission	49 cm at admission	NM	—
4	*ROGDI*	M	6 years	5 months	At term	BW 3200 g 19 kg at admission	116 cm at admission	48 cm at admission	NM	—
5	*ROGDI*	M	14 years	10 months	NM	NM	NM	NM	NM	NM
6	*ROGDI*	M	6.8 years	9 months	Preterm	BW 6.6 kg	72 cm	45 cm	NM	—
7	*ROGDI*	F	6 years	13 months	At term	3500 g	NM	NM	NM	—
8	*ROGDI*	F	24 years	12 months	At term	3500 g	NM	NM	NM	—
9	*ROGDI*	M	16 years	9 months	At term	3500 g	NM	NM	NM	—
10	*ROGDI*	M	17 years	6.5 months	At term	3250 g	NM	NM	NM	—
11	*ROGDI*	F	16 years	12 months	At term	3250 g	NM	NM	NM	—
12	*ROGDI*	M	14 years	42 months	At term	3500 g	NM	NM	NM	—
13	*ROGDI*	F	16.5 years	9 months	At term	2400 g	NM	NM	NM	—
14	*ROGDI*	M	14.5 years	9 months	At term	2500 g	NM	NM	NM	—
15	*ROGDI*	F	2 years (deceased)	Birth	At term	2300 g	NM	NM	NM	—
16	*ROGDI*	F	19.5 years	9 months	At term	2800 g	NM	NM	NM	—
17	*ROGDI*	M	16.5 years	10 months	At term	3140 g	NM	NM	NM	—
18	*ROGDI*	F	15 years	9 months	At term	3500 g	NM	NM	NM	—
19	*ROGDI*	M	3.5 years	9 months	At term	3800 g	NM	NM	NM	—
20	*ROGDI*	M	4.5 years	11 months	At term	3500 g	NM	NM	NM	—
21	*ROGDI*	F	3.5 years	12 months	At term	NM	NM	NM	NM	—
22	*ROGDI*	M	22 years	7 months	At term	NM	NM	NM	NM	—
23	*ROGDI*	M	N MONTHS	7 months	NM	NM	NM	NM	NM	—

Abbreviations: F: female, M: male, NM: not mentioned, HC: head circumference, Y: years M: months, BW: birth weight, KG: kilograms, G: grams. (+) indicates the presence of the variable. (—) indicates the absence of the variable.

patients experienced a delay in the domain. Detailed data on developmental history are presented in Table 3.

Referring to the patients` clinical spectrum, amelogenesis imperfect was present in 20 patients while the remaining couple of patients were not mentioned (cases 15 and 23). Yellowish teeth were seen in 21 patients. Case number 15 did not mention the presence or absence of yellowish teeth. Dental carries were reported among five patients. Brain abnormalities, which included microcephaly, macrocephaly, holoprosencephaly, infantile hypotonia, spasticity, and ataxia, were reported among 11 patients (50%) while three patients (13.6%) had no forms of brain abnormalities. Eye abnormalities, that included nystagmus, hypertelorism, microphthalmia, esotropia, and strabismus, were observed among four patients (18.1%). Head and face deformities, which included scalp defect, sloping forehead, broad and flat nose, cleft lip and/or palate, highly arched palate, and protruding lower lip, were seen in two patients (9.09%). Failure to thrive was reported among four patients (18.1%) while others did not describe or mention any failure to thrive. Behavior problems were reported among seven patients (31.8%). Detailed data are summarized in Table 4.

As for the electrographical and neuroradiological data, six patients (27.2%) had an abnormal EEG in comparison to six patients (27.2%) who had a normal EEG. Others either did not perform an EEG or were not mentioned in their studies. MRI was abnormal among seven patients (31.8%) in comparison to five patients with normal MRI. Others either did not perform an MRI or were not

Table 2. *Seizure semiology, ASMs, and response to treatment.*

Case no.	Semiology	ASMs	Response
1 (present case)	Focal	Levetiracetam	Controlled
2	GTC	Levetiracetam	Controlled
3	GTC, Partial myoclonic	Phenobarbital and levetiracetam	2 seizures per month
4	GTC	Clobazam, Ethosuximide, and Primidone	NM
5	NM	Phenytoin and clobazam	Controlled
6	Focal tonic-clonic with secondary generalization	Levetiracetam	Controlled
7	Not specified	Unspecified ASM	Controlled
8	Not specified	Unspecified ASM	Refractory
9	Not specified	Unspecified ASM	Refractory
10	Not specified	Unspecified ASM	Partial control
11	Not specified	Unspecified ASM	Partial control
12	Not specified	Unspecified ASM	Refractory
13	Not specified	Unspecified ASM	Controlled
14	Not specified	Unspecified ASM	Refractory
15	Not specified	Unspecified ASM	NM
16	Not specified	Unspecified ASM	NM
17	Not specified	Unspecified ASM	NM
18	Not specified	Unspecified ASM	NM
19	Not specified	Unspecified ASM	NM
20	Not specified	Unspecified ASM	NM
21	Not specified	Unspecified ASM	NM
22	Not specified	Unspecified ASM	NM
23	NM	NM	Refractory

Abbreviations: GTC: generalized tonic-clonic, NM: not mentioned.

mentioned in their studies. Detailed data are presented in Table 5.

Discussion

KTS is a rare syndrome characterized by a unique triad of amelogenesis imperfecta affecting both primary and secondary teeth and causing yellow or brown discoloration of the teeth, early onset seizures, and progressive mental retardation that affects the developmental process of children (1,13). Previously, there were investigations on KTS that included their clinical features without specifying any differences or special hallmarks for *ROGDI*-associated mutation (7,13). Such studies also reflected that *ROGDI* mutations have only been identified in typical KTS cases and that the atypical KTS phenotype is negative for *ROGDI* mutations (6). Mory et al. 2014 (8) reported that among affected populations the pathognomonic pleomorphic characteristics are constant, however even within a single inbred family, the onset and severity of epileptic and neurodegenerative symptoms are variable. Nonetheless, despite its unique triad and consistent phenotype, variability among the patients does exist. Even with the complexity of the phenotype, it is suggested that mutations in the *ROGDI* gene are linked to a specific pattern of clinical features (6). This disorder as described initially is almost always diagnosed during the child's first convulsive episode (3) echoing the findings of the current study in which the majority of the patients are reported to be diagnosed very early in their life and similar to the case we present. Furthermore, the mean duration of onset of seizure amongst reported patients was 7 months, slightly earlier than the onset of seizures in our patient. It should be also noted that despite the early onset of seizure; no correlation was established with the rapid progression of the condition (14). KTS has been firmly associated with consanguineous marriages (15). Despite this, no consistence findings were reported in terms of complicated pregnancies nor an increase in pre-term delivery incidence. Seizure details were described in a limited number of patients with a confirmed *ROGDI* mutation. However, 4 patients (case numbers 2, 3, 4, and 6) experienced GTC seizures (5,14). Similarly, our patient experienced a fever that provoked a GTC seizure. Unlike the case reported by Morscher et al. (5) where valproic acid was found unsuccessful in controlling the seizures, our patient made significant improvement in valproic acid when he had no seizures for two years and the treatment was fully withdrawn. However, in different experiences, a patient was reported to become seizure free after experiencing persistent seizures upon switching

Table 3. *Assessment of developmental milestones.*

Case no.	Developmental delay			
	Cognitive	Sensorimotor	Speech and language	Socioemotional
1 (present case)	+	+ (mild ataxia)	+	—
2	+	+	+	+
3	+	+	+	+
4	+	+	+	+
5	NM	+	NM	NM
6	+	+	+	+
7	+	—	+	NM
8	+	+	+	NM
9	+	-	+	NM
10	+	+	+	NM
11	+	—	+	NM
12	+	—	+	NM
13	+	—	+	NM
14	+	+	+	NM
15	NM	NM	NM	NM
16	+	+	+	NM
17	+	+	+	NM
18	+	+	+	NM
19	+	+	+	NM
20	+	+	+	NM
21	+	+	+	NM
22	+	+	+	NM
23	+	+	NM	NM

Abbreviations: NM: not mentioned. (+) indicates the presence of the variable. (—) indicates the absence of the variable.

phenobarbital, valproic acid, and oxcarbazepine to levetiracetam (7). The underlying mechanism and variable responses remain unknown. Other studies further validated similar clinical outcomes by reporting complete control of seizures after administrating levetiracetam (5,14). Seizure control was also observed in a patient who used dual therapy of phenytoin and clobazam (16). Unfortunately, until the publishing of this work, evidence remains inconclusive regarding the most appropriate treatment modalities to administer on patients with KTS with no enough data to support such an approach. As future direction in this aspect, it is also important to report any side effects or unexpected clinical events. Treatment should primarily focus on managing symptoms and improving the quality of life for affected individuals. Merely treating seizures, which are a prominent feature of KTS, with the use of appropriate medications can improve outcomes and patients' clinical course. This is represented in our reported patient as well as in several other literature cases (5,14,16). Furthermore, early intervention programs, including occupational therapy, speech therapy, and physical therapy, are essential in addressing developmental delays and improving motor skills, communication, and cognitive abilities. Moreover, developmental delay was a distinguishable feature. Most notably, the cognitive abilities of the vast majority of the patients were compromised. One important theory previously presented was a possible interaction between the *ROGDI* variant, which is widely expressed in the brain, and a protein termed *DISC1* which is involved in diverse cytoskeletal functions by impairing metabolic functions of astrocytes leading eventually to cognitive dysfunction (17,18). However, these findings were drawn from animal-based studies. Despite this and in the general context, *DISC1* protein can serve as a valuable molecular tool to advance our understanding of the pathophysiology of KTS, a conclusion that has been previously mentioned in the literature (19–22). Nonetheless, investigating the underlying genetic causes of KTS is a promising avenue for developing targeted therapies. Lastly, in terms of neuroradiological findings, there were no specific patterns on EEG and MRI for reported patients.

Conclusion

In conclusion, the study investigated patients specifically carrying the *ROGDI* variant. Current understanding of the condition was echoed throughout this study despite several drawbacks due to the limited number of reported cases which oppose a challenge to identify and draw conclusive evidence. In one important aspect, there were conflicting reports on the efficacy of different ASMs and the adequate

Table 4. *Assessment of clinical manifestations.*

Case no.	Teeth abnormalities			Brain abnormalities	Eyes abnormalities	Head and face deformities	Failure to thrive	Behavioral problems
	Amelogenesis imperfect	Yellowish	Dental carries					
1 (present case)	+	=	+	—	—	—	—	+
2	+	+	+	—	+	NM	NM	+
3	+	+	+	+	+	NM	+	+
4	+	+	+	+	+	+	+	+
5	+	+	+	—	-	+	NM	+
6	+	+	+	+	+	-	NM	+
7	+	+	NM	—	NM	NM	NM	NM
8	+	+	NM	+	NM	NM	NM	+
9	+	+	NM	NM	NM	NM	NM	+
10	+	+	NM	+	NM	NM	NM	NM
11	+	+	NM	NM	NM	NM	NM	NM
12	+	+	NM	NM	NM	NM	NM	NM
13	+	+	NM	NM	NM	NM	NM	NM
14	+	+	NM	NM	NM	NM	NM	NM
15	NM	NM	NM	+	NM	NM	+	NM
16	+	NM	NM	+	NM	NM	NM	NM
17	+	NM	NM	+	NM	NM	NM	NM
18	+	NM	NM	+	NM	NM	NM	NM
19	+	NM	NM	NM	NM	NM	NM	NM
20	+	NM	NM	NM	NM	NM	NM	NM
21	+	NM	NM	NM	NM	NM	NM	NM
22	+	NM	NM	+	NM	NM	NM	NM
23	NM	NM	NM	+	NM	NM	+	NM

Abbreviations: NM: not mentioned. (+) indicates the presence of the variable. (—) indicates the absence of the variable. Brain abnormalities included the presence of one or more of the following manifestations: Microcephaly, macrocephaly, holoprosencephaly, infantile hypotonia, spasticity, ataxia Eye abnormalities included the presence of one or more of the following manifestations: Nystagmus, hypertelorism, microphthalmia, esotrophy, strabismus. Head and face deformities included the presence of one or more of the following manifestations: Scalp defect, sloping forehead, broad and flat nose, cleft lip and/or palate, highly arched palate, protruding lower lip.

treatment modality to treat such cases, this aspect remains inconclusive despite its importance. Potential hallmarks continue to be established including the historically reported triad and pattern of developmental delay. New horizons including our understanding of the deterioration of patients' cognitive abilities are becoming promising to understand with the theories of *ROGDI* mutation. Current evidence can be validated and a delineation of clinical and molecular findings is achievable with the aid of additional reporting for similar cases.

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List of Abbreviations

ASM	Anti-seizure medications
EEG	Electroencephalogram
GTC	Generalized tonic-clonic
KTS	Kohlschütter–Tönz syndrome
MRI	Magnetic resonance imaging
NGS	Next generation sequencing

Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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Consent for publication

Informed consent was obtained from the patients.

Table 5. *Electrographical and neuroradiological summary.*

Case no.	EEG abnormities	MRI abnormities
1 (present case)	+	—
2	+	+
3	—	+
4	NM	+
5	NM	NM
6	+	-—
7	—	+
8	NM	+
9	—	+
10	+	-—
11	NM	NM
12	+	NM
13	NM	NM
14	NM	NM
15	NM	NM
16	NM	NM
17	+	+
18	—	NM
19	+	—
20	—	—
21	—	—
22	NM	NM
23	NM	NM

Abbreviations: NM: not mentioned. (+) indicates the presence of the variable. (—) indicates the absence of the variable.

Ethical approval

The study obtained ethical approval from the Unit of Biomedical Ethics Research Committee at the Faculty of Medicine, King Abdulaziz University (Reference No. 265-23).

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