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A rare neurodegenerative disorder with a novel mutation in *ROGDI* and Rett- like phenotype: Kohlschütter- Tönz syndrome

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Abstract

Kohlschütter-Tönz syndrome (KTZS) is a rare neurodegenerative disorder that presents with seizures, developmental delay, psychomotor regression, hypoplastic dental enamel morphology characteristic for amelogenesis imperfecta, and dysmorphologies. Genetic analysis has identified loss of function mutations within the coding region of the *ROGDI* and SLC13A5 genes in KTZS. In this report, we documented the clinical, radiological, electroencephalographic, and genetic results of a 3.5-year-old Turkish girl, born to nonconsanguineous parents, who was the first patient diagnosed with KTZS in Turkey. The patient presented with Rett syndrome-like phenotype, neurodevelopmental delay, refractory seizures, and amelogenesis imperfecta. After obtaining informed consent, chromosomal DNA was extracted from the peripheral blood of our patient and her parents. To investigate the molecular diagnosis of the patient, the clinical exome sequencing was performed. The Sanger sequencing analysis was performed for all of the family members for the validation and segregation of this mutation. Pub Med/Medline, Web of Science, and Google Scholar were also searched to find all of the published data on KTZS. The literature comprises 18 published studies about KTZS. The genetic analysis of our patient revealed a novel homozygous c.201-1G>T mutation in the *ROGDI* gene. The same mutation was also found to be heterozygous in her mother and father. The mutation caused alternative splicing of the *ROGDI* translation and resulted in a disruption of the *ROGDI* protein.

Keywords: Amelogenesis imperfecta; Neurodevelopmental delay; Rett-like phenotype; Refractory epilepsy; Novel ROGDI mutation; Kohlschütter-Tönz syndrome

INTRODUCTION

Kohlschütter-Tönz syndrome (KTZS) is a very rare autosomal recessive neurodegenerative disorder in which the causative mutations are in the *ROGDI* gene on chromosome 16p13.3 or the SLC13A5 gene on chromosome 17p13.1.[1-3] Kohlschütter-Tönz syndrome was first published with phenotypic features like progressive global developmental delay, seizures, and the absence of a normally mineralized enamel coating the teeth, in 1974, by Kohlschütter et al.[4] To date, few reports have been added to the literature. In addition to neurodevelopmental delay, seizures, and yellowish teeth due to amelogenesis imperfecta (AI), these cases have been reported with dysmorphic features, spasticity, early onset intractable seizures, and ataxia.[5-8] In this report, we present a 3.5-year-old Turkish girl diagnosed with KTZS with novel genetic and clinical features to increase the awareness of clinicians and update the literature. This study was approved by the Doctor Sami Ulus Pediatric and Training Hospital (Turkey) local ethics committee, and informed consent was obtained for each member of the family before each of the experiments. Pub Med/Medline, Web of Science, and Google Scholar were also searched to find all of the published data on KTZS.

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CASE REPORT

A 3.5-year-old Turkish girl, whose parents had no consanguinity, was born at term by caesarean section. Her weight at birth was 3.127 kg (–0.48 standard deviation, SD) at 39 weeks and 3 days of amenorrhea from the first and only pregnancy of the 18-year-old mother, without any complications. The length of the baby was 51 cm (+0.44 SD) and the occipital-frontal circumference (OFC) was 33 cm (–1.21 SD) at birth. The patient was first admitted to the pediatric neurology department with the complaint of neurodevelopmental delay and hypotonia at the age of 6 months. During her neurological examination, she was microcephalic (OFC: 41 cm, –2.5 SD). As an infant, she did not smile. She never vocalized. Her motor examination revealed significant axial and peripheral hypotonia. Her deep tendon reflexes were absent. She never developed the ability to roll. Dysmorphic features such as micrognathia, high arched palate, hypertelorism, and flat occiput were detected. In the differential diagnosis, congenital muscular dystrophy, congenital myopathies, spinal muscular atrophy, SJögren-Larsson syndrome, congenital disorders of glycosylation, mitochondrial disorders, and peroxisomal disorders were all discussed and a detailed neurological examination, metabolic tests, muscle biopsy, and neuroimaging findings excluded these diseases. During the follow-up period, at 9 months of age, refractory cluster complex, which are partial seizures lasting for almost 30–40 s, were added to her neurological manifestations. The refractory seizures were brought under control with dual antiepileptic treatment, phenobarbital, and levetiracetam at the age of 3. Rett-like phenotypic features, such as steorotypic swinging, hand rubbing, and also drooling were detected as neurological manifestations at the same time. Her initial and serial electroencephalographic findings revealed right fronto-temporal discharges and secondary generalized epileptic activities. Brain magnetic resonance imaging (MRI) at the age of 2 years and 11 months showed diffuse cerebral atrophy and a small volume of occipital lobes (Figure 1A). Delayed myelination was remarkable, especially on T2-weighted images. Myelination was not observed in structures other than the internal capsules, corpus callosum and occipital white matter, including the optic radiation. No vermian or basal ganglia atrophy was observed (Figure 1B). At her last visit, at the age of 3 years 6 months, she was severely microcephalic (OFC 45 cm, –3.8 SD) with dysmorphic features, such as micrognathia, hypertelorism, low-set ears (Figure 2), axial hypotonic with absent deep tendon reflexes, and unable to walk independently. She had no use handheld, steorotypic movements, and hypersalivation (supplementary video). As she had hypersalivation and was scratching her teeth with her hands, the oro-dental examination that was offered revealed no abnormalities in the tooth number and size, but abnormalities of the enamel affecting the primary dentition were present**.** A

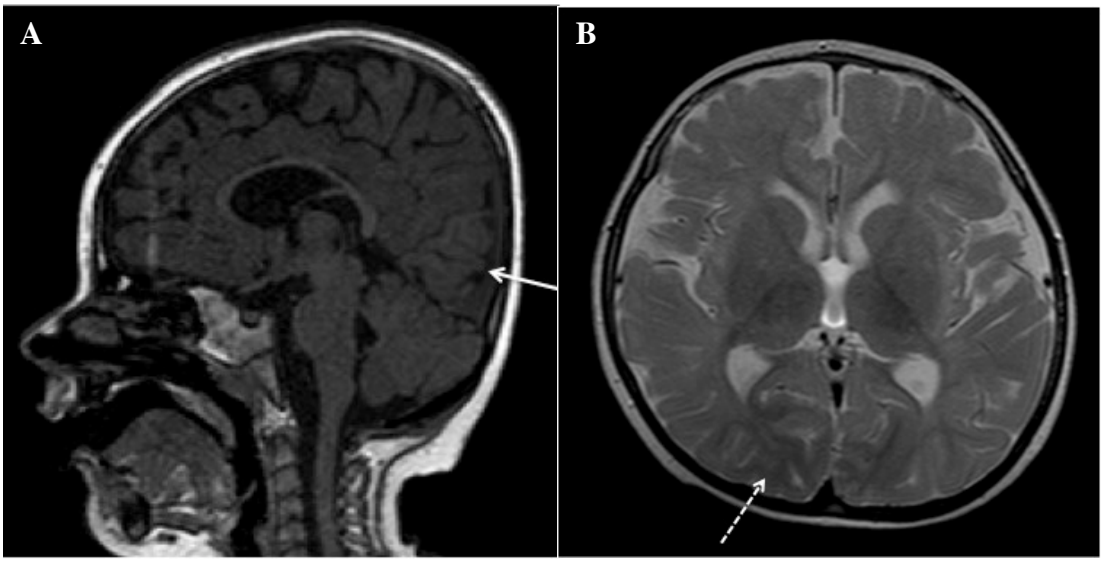

Figure 1. MRI obtained at 2 11/12 years of age. Sagittal T1-weighted image (WI) (A) shows thin corpus callosum and small occipital lobe (thin arrow, A). Please note that the vermis is well-developed. Axial T2WI (B) shows delayed myelination, while it's well observed in the occipital lobe (dashed arrow, B).

Figure 2. Dysmorphic features of the patient showing micrognathia, hypertelorism and low set ears.

diagnosis of hypomineralized/hypomature AI was proposed. Because of her medical and behavioral handicaps, dental examinations were performed under general anesthesia. The diagnosis of KTZS was confirmed through clinical exome sequencing (CES), which revealed a novel homozygous mutation at the age of 3 years and 6 months.

Genetic analysis

Methods

The clinical exome solution by Sophia Genetics® (Saint Sulpice, Switzerland) was performed using the Nextseq 500 next-generation sequencing (NGS) platform (Illumina, San Diego, CA) according to the manufacturer's instructions for the molecular diagnosis of our patient. For the variant filtering process, we considered only nonsense and missense variants, indels, and variants at canonical splice sites, excluding variants with a minor allele frequency greater than 0.01 in different public and local resources.

To validate the segregation of this mutation, Sanger sequencing analysis was performed for all of the family members. Written informed consent was obtained from the parents of the patient for publication of this report with accompanying images and results.

Results

The clinical exome solution by Sophia Genetics® (Saint Sulpice, Switzerland) was performed for the molecular diagnosis of the patient. A homozygous novel c.201-1G>T splice site mutation was detected in the *ROGDI (NM_024589.2)* gene (supplementary diagram). In addition, this variation was not reported in the gnomAD (v2.1.1), Exac, and in-house databases, but it is listed as a 'disease causing' mutation on several in silico databases such as Mutation Taster, DANN, Human Splicing Finder (HSF). The mutation located at the end of the intron 3 of *ROGDI*, and probably affected the transcription of exon 4 by changing the acceptor site of exon 4. HSF interpreted as 'most probably affecting splicing', Mutation Taster predicted as 'disease causing' and DANN score was 0.995; that means 'damaging'. As expected, all programs predicted the destruction of the protein. The same mutation was also found to be heterozygous in the mother and father.

DISCUSSION

The *ROGDI* gene, located on chromosome 16, is composed of 11 coding exons. The encoded protein is 28,700 long and is described as leucine zipper domain-containing protein.[9] In this paper, we report a new mutation in the *ROGDI* gene. This is the first report of a mutation in the *ROGDI* gene in a Turkish patient; presented with Rett-like phenotypic features, intractable seizures, neurodevelopmental delay, psychomotor regression, and AI. Other mutations described in the literature include deletions, duplications, splicing, and frameshift mutations[10-12]; however, this is the first case presented with Rett-like phenotypic features associated with this mutation.

Table 1 summarizes the previously reported patients with KTZS to date. Table 2 summarizes the KTZS patients, including our patient, with confirmed ROGDI gene mutations. To date, 18 pedigrees have been reported as KTZS. Twelve mutation positive families had been reported prior to our patient and her family. Based on the mutation-confirmed data results, 33 cases from 13 families have been documented. Patients from Austria, Switzerland, Germany, Sicily, Moracco, Mali, Druze, Causian, and India had been reported prior to our Turkish patient. The male to female ratio was 1.2/1. Core clinical features of the patients were seizures (mostly refractory), neurodevelopmental delay, and AI. All the patients (33/33) (100%) had core clinical features. The starting age of the seizures was between birth and 42 months of age. All of the patients (33/33) (100%) had speech and intellectual impairment.

Table 1: The summary of patients with the diagnosis of Kohlschütter – Tönz sydrome from pubmed search

References	Number Of Cases / Sex	Consanguinity	Ethics	Clinical Findings	Age Of Start Seizure	Tooth Findings	MRI	Type Of Gene Mutation
Aswath *et al*, 2018[12]	1 M	Yes	Indian (Tamil Dravian)	GDD Seizures (Refractory) Laernin Difficulties, ADHD No dysmorphic features high-arched palate	10 Mo	Enemal hypoplasia AI	Absent	ROGDI Gene Hom C402 C>T (Y134 STOP)
Schossig *et al*, 2017[3]	10 / From 5 Families 3 M 7 F	Yes/No	The Caribbean Europe (Italy, Germany, The Netherlands)	GDD Seizures Neonatal convulsion İnfantile hypotonia Spasticity Ataxic dystonic gait Speech delay / No Language Strabismus (+1) Cerebellar ataxia (+1)	Birth	Yellow colored teeth Enemal hypoplasia AI	No remarkable findings	SLC13A5 Gene C.997C>T hom C.203C>A het +C.434C>A Het C.103 1g>A het +C.1276-1g>A het C.425c>T het + C.655G>A het C.680 C>T Hom
Morscher *et al*, 2017[10]	1 M	No	Causian	GDD Seizures Mild hip dysplasia Truncal hypotonia Jerk nystagmus Pectus excavatum Joint hypermotility No dysmorphic features	9 mo	Yellow discoloration and carious changes in front teeth (first noted at the age of 2) – Complete enamal loss and brownish- black discoloration	No structural malformations	Sanger sequencing homozygous splice site mutation c.256-2a>c.
Huckert *et al*, 2014[14]	1 F	?	Malian	GDD Seizures Hypotonia Strangulated inguinal hernia Right-sided neglect Ataxic gait Speech delay Dysmorphic features (frontal bossing, thickened protruding lower lip, genital hypoplasia) Aggresive, impulsive behaviour	3rd week of lif	Enemal dysplasia AI	Absent	DNA sequencing homozygous C.117+1G>T (Chr16 (GRCh37) G.4852382 C>A)

References	Number Of Cases / Sex	Consanguinity	Ethics	Clinical Findings	Age Of Start Seizure	Tooth Findings	MRI	Type Of Gene Mutation
Mory *et al*, 2014[13]	8 M 8 F	5 families; 3 of consangious, 1 originated from same village	Northen Israel	GDD Seizures (Refractory) Microcephaly No speech	6.5 mo – 42 Mmo	Yellow colored teeth AI	Cranial MRG performed for 7 patients and showed cerebral atrophy in 4.	ROGDI gene hom c57C>T(all patients)
De Souza *et al*, 2014[15]	No data avaible / Only abstract							ROGDI gene mutation was not detected
Gonzalez-Arrigada *et al*, 2013[16]	1 M	Absent	Absent	GDD Seizures Hyperactivity Speech delay İmpulsive behaviour ADHD Learning problems Dysmorphic features (slightly palpabral fissurs, low ear and hair implatation, coarse hair, hypertrichosis)	4 Yrs? 8 Yrs	Yellow colored teeth AI	Absent	Absent
Schossig *et al*, 2012[17]	2 F 2 M	Yes	Swiss Moraccan	GDD Seizures (one patient with infantile spasms) No language Spasticity (+1) Hip dislocation (+1) Scoliosis (+1)	6 mo - 12 mo	Yellow Colored Teeth AI	Atrophy of cerebellar vermis (+1) Delayed myelinisation (+1)	ROGDI gene hom c229_230del (+1)
Tucci *et al*, 2013[2]	3 M 1 F		Germany (1 M) The Netherlands	GDD Seizures Spasticity (+1) No language (+2) Microcephaly Hypermotility of joints Hip dislocation Scoliosis Clumsiness	7 mo- 18 mo	AI	Atrophy of cerebellar vermis (+1) and small pons	ROGDI Gene hom c507delC hom c49-37-46-30del
Haberlandt *et al*, 2006[8]	1 M	Neighboring villages	Australia	GDD Seizures Dysmorphic features (asymetric skull, coarse hair, upslating palpebral fissurs, smooth filtrum)	8 mo	Yellow Colored Teeth AI	Cerebellar vermiş hypoplasia Moderate enlargement of ventricules	Absent

References	Number Of Cases / Sex	Consanguinity	Ethics	Clinical Findings	Age Of Start Seizure	Tooth Findings	MRI	Type Of Gene Mutation
Donnai *et al*, 2005[31]	1 M 1 F (NF-1)	?	English	GDD Seizures No language Microcephaly Feeding problems with multipl food intolerance	1 mo	Yellow Colored Teeth AI	Vermis hypoplasia and enlarged ventricule	Absent
Wygold *et al*, 1996[32]	1 M	?	?	GDD Seizures	6 mo	AI	Cerebral atrophy	Absent
Musumeci *et al*, 1995[7]	1 M 1 F (siblings)	Yes	Sicilian	GDD Seizures Spasticity No Language (+1) Secondary Microcephaly Dysmorphic Features (Broad Thumbs And Toes)	2 mo- 10 mo	Yellow Colored Teeth Enemal Hypoplasia AI	Vermis hypoplasia and asymmetric dilatation of the ventricules and enlarged ventricules (+1)	Absent
Guazzi *et al*, 1994[6]	2 M 1 F 3 siblings	Yes	Sicilian	GDD Seizures Ataxia Dementia (moderate) EEG abnormalities		Yellow Colored Teeth Enemal Hypoplasia AI	Periventriculer White matter gliosis and enlarged ventricules	Absent
Petermöller *et al*, 1993[33]	1 M 1 F	?	Germany			AI		Absent
Zlotogora *et al*, 1993[5]	1 M 1 F	Yes	Israel	GDD Seizures Spasticity (+1) Congenital nystagmus (+1)	12 mo -3 yrs	AI	CT scan is normal	Absent
Christodolou *et al*, 1988[34]	4 M 2 F	Close-knit town	Sicilian	GDD Seizures	7 mo- 22 mo	AI	Absent	Absent
Kohlschütter *et al*, 1974[4]	5 M (brothers)	Yes	Swiss	GDD Seizures Spasticity	11 mo - 4 yrs	AI	Microcephaly and enlarged ventricules in 1 patient	Absent

Abbreviations: GDD: global develeopmental delay,; M: Male,; F: Female; Hom: Homozygous; Het: Heterozygous; AI: Amelogenesis imperfecta; ADHD: Attention deficite hyperactivity disorder; Nf-1: Neurofibromatosis 1 (only one patient); +1 : only one patient; MRI: magnetic resonance imaging

Table 2: The summary of KTZS patients with confirmed *ROGDI* gene mutations

Pedigree	Reference	Mutation	Protein Effect	Major Clinical and Demografic Features
P 1	Schossig *et al*., 2012[1]	c.286C>T (homozygote)	p.Gln96Term	Noc: 1 (M) Ethnicity: Austrian Consanguinity: None Core features Saos: 5 mo
P 2	Mory *et al*., 2012[9]	c.469C>T(homozygote)	p.Arg157Term	Noc: 14 (7F,7M) Ethnicity: Druze Consanguinity: + Core features Saos: Birth-42 months
P 3	Schossig *et al*., 2012[1]	c.532-2A>T	Splice site	Noc: 1 (F) Ethnicity: Swiss Consanguinity: distant relatent Core features Saos: 6 mo
		c.531+5G>C	Splice site	
P 4	Schossig *et al*., 2012[1]	c.229_230delCT (homozygote)	Small Deletion	Noc: 2 (F, M) Ethnicity: Moraccon Consanguinity: + Core features Saos: 4,12 mo respectively
P 5	Tucci *et al*., 2013[2]	c.46+37_46-30delGGCGGGC (homozygote)	Small Deletion	Noc: 2 affected siblings (1 M, F)(Musimeci *et al*.; 1995) Ehtnicity: Sicilian Consanguinity: + Core features+broad thumbs/toes Saos: 2-10 mo
P 6	Tucci *et al*., 2013[2]	c.45+9_45+20delCGCGGGCCAGCG	Small Deletion	Noc: 2, 1 affected proband (Petermoller *et al*., 1993) Ethnicity: German Consanguinity: None Core features Saos: 8 mo
P 7		c.507delC	Small Deletion	Noc: 6 siblings (Christodolou *et al*., 1988) Ethnicity: Sicilian Consanguinity: + Core features: + Saos: 7-22 months
P 8		c.507delC		Noc: 1 Ehnicity: German Consanguinity: None Core features Saos: 7 mo
P 9	Tucci *et al*., 2013[2]	c.366dupA (homozygote)	Small İnsertion	Noc: 1 (M)(Schossig *et al*., 2012) Ethnicity: German Consanguinity: None Core features Saos: 11 mo
P 10	Huckert *et al*., 2014[14]	c.117+1G>T(homozygote)	Splice site	Noc: 1 (F) Ethnicity: Malian Consanguinity: None Core features+dysmorphology Genital hypoplasia Saos: 3 rd week of life
P 11	Morscher *et al*., 2017[10]	64 kb deletion	Gross Deletion	Noc: 1 (M) Ethnicity: Caucasian Consanguinity: None Core features Saos: 9 mo
		c.256-2A>G	Splice site	

Pedigree	Reference	Mutation	Protein Effect	Major Clinical and Demografic Features
P 12	Aswath *et al*., 2018[12]	c.402C>T(homozygote)	p.Tyr134Term	Noc: 1 (M) Ethnicity: Indian Consanguinity: + Core features Saos: 10 mo
P 13	This study	c.201-1G>T(homozygote)	Splice site	Noc: 1 (F) Ethnicity: Turkish Consanguinity: None Core features+ Rett- like phenotype Saos: 9 mo

Abbreviations:
M: Male; F: Female; P: Pedigree; Mo: Months; Core features: Neurodevolopmental delay, seizures, amelogenesis imperfecta; Noc: Number of cases; Saos: Starting age of seizure

Fourteen of 33 patients (42.4%) were ambulatuar. Four of 33 patients (12.1%) had psychomotor delay since birth while the remainder (29/33) (87.8%) had normal development until the onset of seizures. Additional features such as genital hypoplasia (n: 1) (3%), short stature (n: 1) (3%), pectus excavatum (n: 1) (3%), hip dislocation (n: 4) (12.1%) and scoliosis (n: 4) (12.1%) have been documented in a few cases. Dysmorphologies such as frontal bossing (n: 1) (3%), a thickened protruding lower lip (n: 1) (3%), a smooth philtrum (n: 1) (3%), slightly palpebral fissures (n:1) (3%), low-set ears (n: 1) (3%), and broad toes and thumbs (n: 2) (6%) coexisted in some of the cases. Some additional and dysmorphic features such as neurofibromatosis type-1, an asymmetric skull, coarse hair and hypertrichosis coexisted in few cases without documented mutations. Our patient had dysmorphic features, such as micrognathia, hypertelorism, flat-occiput, and low-set ears.

Splicing, small and gross deletions and small insertions were responsible for LOF of *ROGDI* gene. The data derived from the literature review revealed that there were 15 mutations in 13 families. All these mutations seriously disrupted the protein structure. The most common of these mutations were indels (6/15) (40%), splice site mutations (5/15) (33.3%), nonsense mutations (3/15) (20%) and a gross deletion (1/15) (6.6%) respectively. The same mutation (c.507delC) was seen in only two different families. The function of the *ROGDI* gene is not absolutely known. The protein is also present in metazoon species, ranging from worms to humans, and is highly conserved.[10-12] These data reveal that it is crucial for survival.

Kohlschütter-Tönz syndrome is caused by homozygous or compound heterozygous mutations in the *ROGDI* gene.[13,14] Our patient was the only child of nonconsanguineous parents with a novel homozygous splice site mutation. Reports of affected sibs and parental consanguinity indicate the autosomal recessive inheritance of KTZS[15], but there were some nonconsanguineous parents in the reports (Table 2). *ROGDI* encodes a leucine-zipper protein as a player in neurogenesis with strong expression in the human brain and spinal cord. This expression pattern of the gene is in line with the disease characteristics relevant to cortical dysfunction and spasticity.[16] In 2016, the SLC13A5 gene mutation was shown in the *ROGDI*-negative group by researchers who previously showed that the mutation in KTZS was related to the *ROGDI* gene. The SLC13A5 gene is known as a cause of early infantile autosomal recessive epileptic encephalopathy. Clinical and histological evaluations have confirmed distinct dental differences between KTZS caused by the *ROGDI* or *SLC13A5* mutation.[3]

Seizures, mental-motor developmental delay, and hypotonia can be explained with impaired neurogenesis in this rare neurodegenerative syndrome. Intellectual disability is related to the severity of seizures; hence, the disorder can thus be considered as an epileptic encephalopathy.[10] Seizures mainly start in the first year of life in the majority of patients, as with our patient. Some authors have emphasized that developmental regression initiated at the same time as the seizures[17], whereas others have emphasized the delay from birth[8], as with our patient. We emphasized that the cognitive decline could be related to refractory seizures, as with our patient. In all mutation-confirmed KTZS patients described before, the first epileptic seizures mostly occured before the age of 1 year and often proofed difficult to treat[18]; as with our patient. For the majority of reported cases; developmental regression has been described following seizure

onset[17] and seizure control has not sufficiently improved the neurodevelopmental retardation in time. We beliewe that neurodevelopmental delay of KTZS patients exist from birth and is noticed by the parents after the onset of clinical seizures. There is not any specific seizure type or EEG pattern for KTZS. Subclinical EEG discharges may be present before the onset of clinical seizures in KTZS patients. Epileptic encephalopathy is a heterogenous group of severe epileptic disorders characterized by refractory seizures and abnormal EEG that leads to neurological impairment and developmental delay.[19] The underlying genetic cause often results in developmental delay in its origin, with the epileptic encephalopathy further adversely affecting development.[18] As many children regress with onset of seizures in KTZS, the disease might be classified as a developmental and epileptic encephalopathy.

Musumeci[7] and Mory *et al*.[9] reported hypoplasia of the cerebellar vermis, enlargement of the lateral ventricules, and cerebral atrophy on the brain MRI. We discovered from the literature research that a thin corpus callosum and white matter loss in the occipital lobe was first reported herein. We hypothesized that these new findings could be related to the delay or hypomyelination of the occipital lobe, associated with the novel mutation in the *ROGDI* gene.

AI is characterized by rough dental surfaces, which are an abnormality of enamel development that show hereditary transmission and affect the structure, amount, and composition of the primary and permanent teeth enamel. These effects result in discoloration of the teeth.[20] Careful examination of the oral cavity added valuable diagnostic clues for the accurate diagnosis of KTZS in our patient, and after a period of time, it was confirmed with a genetic analysis.

Rare diseases that manifest with neurological symptoms and dental abnormalities, such as tubero sclerosis and SJögren Larsson syndrome, have been previously defined.[21] As our patient had axial hypotonia without deep tendon-reflexes, refractory epilepsy, and Rett-like phenotypic features, CDKL5 mutations[22], mitochondrial disorders with axonal involvement[23], and congenital musculer dystrophy-mitochondrial forms[24] without enamel defects were discussed in the differential diagnosis and all of them were excluded.

The function of the *ROGDI* protein and the link between the dental and brain abnormalities are not absolutely understood. *ROGDI* was also transcribed during mouse and brain development.[25] *ROGDI* was also expressed in the cap stage of odontogenesis in E 14.5 mouse embriyos.[26] These data suggest that *ROGDI* is present and may play a role in brain formation, homeostasis, and odontogenesis. Some authors found wide expression of *ROGDI* gene in multiple human tissues, including adult brain, spinal cord, peripheral blood, heart and bone marrow. Highest expression was found in the spinal cord and adult brain. Lower expression was found in many tissues, including fetal brain.[9] There may be an underlying epigenetic triggering risc factor during maturation of the brain in the pathophysiological pathways of the disease. The genetic loci of *ROGDI* gene (16p13.3) is co- localized to one of the Rett-syndrome like diseases genes *(GRIN2A)*. *GRIN2A* located in 16p13.2 is noted in focal epilepsy with or without cognitive impairment.[27] We emphasize that, these data may be releated with the fact that why our patient had some Rett-like phenotypic features.

ROGDI gene may modify the function of *GRIN2A*, which encodes the GluN2A subunits. These subunits showed varying expression throughout the brain both spatially and temporally.[28,29] GluN2A subunits are a part of NMDAR (N- methyl- D- aspartate receptor) complex; a-ligand-gated ionotropic glutamate receptor, that plays important roles in normal brain development, learning, motor and sensory function, developmental changes in behavior, synaptic function and seizures[30], as with our patient. We believe that, the functional analysis of *ROGDI* mutations may help to highlight the accurate pathophysiological pathways of KTZS in future studies.

Rett-like phenotypic features (first reported in this literature), refractory seizures, neurodevelopmental delay, and enamel structure and color abnormalities can be clinical clues of underlying KTZS. Careful examination of the oral cavity in neurodegenerative diseases and refractory seizures should be the rule. Collaborative analysis, an interdisciplinary approach and multidisciplinary health care centers are needed for this rare neurodegenerative syndrome.

In conclusion, this study was the first to report a case of KTZS in a Turkish family with a novel mutation in the *ROGDI* gene presented with neurodevelopmental delay, refractory seizures, AI, and Rett-like features.

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DISCLOSURE

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