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A SOUTH INDIAN CASE OF KOHLSCHUTTER-TONZ SYNDROME(KTS) WITH SPEECH ABNORMALITY

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Abstract

Background: Kohlscutter-Tonz syndrome (KTS) is a rare autosomal recessive genetic disorder first described in 1974, characterized by seizures, intellectual disability, and abnormalities of teeth and other organs. It is caused by pathogenic variants in the ROGDI gene, with only 44 confirmed cases reported to date.

Objective: Investigate the genetic cause and natural history of an affected South Indian patient from a consanguineous family to inform the diagnosis and management of KTS.

Methods: Targeted gene sequencing of clinically relevant genes was performed using custom capture and Illumina sequencing. Sequencing reads were aligned to GRCh38, and variants called with GATK, then annotated using VariMAT, ClinVar, OMIM, and HGMD. Anti-seizure medications, therapies, and multidisciplinary management strategies used for 44 patients with Kohlscutter-Tonz syndrome were reviewed as a basis for tailored treatment.

Results: Targeted sequencing identified a novel homozygous ROGDI frameshift variant (p. Thr202AsnfsTer26) in the proband. Analysis of 44 published KTS patients found anti-seizure medications-controlled seizures in 10-50% of cases. The prognosis is usually poor due to refractory epilepsy, developmental regression, and early mortality.

Conclusion: This case adds to knowledge of the molecular basis and phenotype of KTS. Symptomatic treatment with anti-seizure medications provides limited efficacy, reflecting a lack of disease-modifying options. Further research on the ROGDI pathway may enable the development of targeted therapies to improve long-term outcomes.

Keywords: Kohlscutter-tonz syndrome, ROGDI gene variants, Refractory epilepsy, Developmental regression, Targeted therapies

INTRODUCTION

Kohlscutter- Tonz syndrome [KTS] also known as amelo-cerebro-hypohidrotic syndrome, is a rare genetic disorder first described in 1974 with autosomal recessive inheritance, caused by homozygous or compound heterozygous mutations in the ROGDI [Rogdi Atypical Leucine Zipper] gene (OMIM*614574) [1]. It was first described in a Swiss family in 1974 by Alfried Kohlschütter and Otmar Tönz [2]. To the best of our knowledge, there are currently 44 patients with a confirmed

ROGDI gene pathogenic variant have been reported, consisting of 25 (56.8%) males and 19 (43.2%) females [3]. Currently, there is no specific treatment available for KTS [4].

CASE HISTORY: In the present study, we have investigated the genetic status of ROGDI in a thirteen-year-old South Indian patient of Dravidian race born to consanguineous parents, presented with clinical indications of seizures, developmental delay, intellectual disability, delayed speech onset & difficulty in speech and abnormal teeth since 6 years of age.

INVESTIGATIONS: All required investigations were done including complete blood picture, serum electrolytes, serum calcium, renal function test, liver function test, and MRI of the brain, and were found to be normal and suggested EEG. He is suspected to be affected by a seizure disorder and has been evaluated for pathogenic variants.

Variant description: A homozygous 1 base pair insertion/duplication in exon 8 of the ROGDI gene (chr16: g.4798112dup; Depth: 173x) that results in a frameshift and premature truncation of the protein 26 amino acids downstream to codon 202 (p. Thr202AsnfsTer26; ENST00000322048.12) was detected. The observed variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1), topped, and in the internal databases. The in-silico prediction# of the variant is damaged by MutationTaster2. The reference region is conserved across species. No other SNV(s)/INDELS or CNV(s) that warrant to be reported were detected. All the genes covered in this assay have been screened for the given clinical indications.

TEST METHODOLOGY: Targeted gene sequencing: Selective capture and sequencing of the protein-coding regions and clinically relevant in the genome is performed. Variants identified in the exonic regions and splice-site are generally actionable compared to variants that occur in non-coding regions. Targeted sequencing represents a cost-effective approach to detect variants present in multiple/large genes in an individual.

DNA extracted from blood was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to a mean depth of >80-100X on the Illumina sequencing platform. We follow the GATK best practices framework for the identification of germline variants in the sample using Sentieon [5]. The sequences obtained are aligned to the human reference genome (GRCh38) using a BWA aligner [6] and analyzed using Sentieon for removing duplicates, recalibration, and re-alignment of indels [5]. Section haplotype caller is then used to identify variants in the sample. The germline variants identified in the sample are deeply annotated using the VariMAT pipeline. Gene annotation of the variants is performed using the VEP program [7] against the Ensembl release 104 human gene model [8]. In addition to SNVs and small Indels, copy number variants (CNVs) are detected from targeted sequence data using the ExomeDepth method [9]. This algorithm detects CNVs based on a comparing of the read-depths in the sample of interest with the matched aggregate reference dataset.

Clinically relevant mutations in both coding and non-coding regions are annotated using published variants in literature and a set of disease databases: ClinVar, OMIM, HGMD, LOVD, DECIPHER (population CNV) and SwissVar [10-16]. Common variants are filtered based on allele frequency in 1000Genome Phase 3, gnomAD (v3.1 & 2.1.1), dbSNP (GCF_000001405.38), 1000 Japanese Genome, TOPMed (Freeze_8), Genome Asia, and our internal Indian population database (MedVarDb v4.0) [17-18]. Non-synonymous variants effect is calculated using multiple algorithms such as PolyPhen-2, SIFT, MutationTaster2, and LRT. Clinically significant variants are used for interpretation and reporting.

SPEECH ASSESSMENT AND SPEECH THERAPY IN TREATMENT STRATEGIES: To provide insights into the treatment strategies for Kohlschutter-Tonz syndrome (KTS), we collected information on the treatment of 44 patients. Except for two patients who only used one anti-seizure medication (ASM), all other patients used at least two ASMs combined with antiepileptic therapy,

and one patient used a maximum of five ASMs. None of the patients received adrenocorticotropic hormone (ACTH) treatment. One patient underwent vagus nerve stimulation (VNS) and adopted a ketogenic diet (KD), but this treatment did not have a satisfactory curative effect, and the patient still had RE. Seven patients (46.7%) responded well to ASMs, and six of them had a seizure frequency reduction of over 50%, with one becoming seizure-free at four years old in Table 1.

Table 1. Treatment Strategies and Outcomes for Kohlschutter-Tonz Syndrome (KTS) Patients

Patient ID	Speech assessment and speech therapy	Response	Seizure Frequency Reduction
1	VPA + CLB	Good	>50%
2	CLB	Good	>50%
3	PHB + VGB	Good	>50%
4	CLB + PHT	Good	>50%
5	PHB + LEV	Good	>50%
6	PMP	Good	-
7	PMP	Good	-
8	VNS + KD	Poor	-

VPA: Valproic Acid, CLB: Clobazam, PHB: Phenobarbital, VGB: Vigabatrin, PHT: Phenytoin, LEV: Levetiracetam, PMP: Perampanel, VNS: Vagus Nerve Stimulation, KD: Ketogenic Diet

The seven patients responded well to different combinations of ASMs: one responded well to VPA combined with clobazam (CLB), one responded well to CLB, one responded well to phenobarbital (PHB), and vigabatrin (VGB), one responded well to CLB combined with phenytoin, one responded well to PHB combined with LEV, and two responded well to PMP. Currently, there is no specific treatment available for KTS. The treatment approach primarily employs a multidisciplinary strategy, focusing on conservative management tailored to the patient's clinical manifestations. This encompasses behavioral therapy, counseling for parents and teachers, speech therapy, and the administration of Anti-Seizure Medications (ASMs).

DISCUSSION:

Kohlscutter- Tonz syndrome [KTS] also known as amelocerebrohypohidrotic syndrome, is a rare genetic disorder first described in 1974 with autosomal recessive inheritance, caused by homozygous or compound heterozygous mutations in the ROGDI [Rogdi Atypical Leucine Zipper] gene (OMIM*614574) [19]. ROGDI is a protein Located in a nuclear envelope, that contains a leucine zipper domain suggesting that ROGDI is a transcription factor; and may be involved in cell proliferation [20]. ROGDI is located on chromosome 16p13.3 with an 864-bp coding region and encodes a protein of unknown function comprising 287 amino acids [21]. In addition, ROGDI is associated with genome stability by regulating the activity of a DNA damage marker (γ-H2AX), which is involved in brain development; neurogenesis; and odontogenesis of dentin-containing teeth [22]. Downregulation of a novel human gene, ROGDI, increases radiosensitivity in cervical cancer cells [23]. The role of ROGDI in tumor radio sensitization has not been investigated. Previous studies have indicated that radiosensitivity is associated with DNA repair and the cell cycle [24]. This syndrome is characterized by amelogenesis imperfecta affecting both primary and secondary teeth and causing yellow or brown discoloration of the teeth. (Two types of amelogenesis imperfecta (AI) have been seen in KTS patients. The first is Hypoplastic which is caused by the enamel being underdeveloped, and the second is hypo-calcified which causes the enamel to be soft and chalky. AI originated as a heterogeneous syndrome but has been observed as homogeneous in the case of KTS), [25] psychomotor delay or regression, seizures starting early in childhood, and microcephaly [26]. Other clinical manifestations such as myopia, ventricular enlargement, dry skin, and altered thumbs/toes also have been described [27], patients could present comorbidities, including ADHD,

ASD, emotional disorders, and language disorders [28]. Although the phenotype is consistent, there is variability, Impaired intellectual development is related to the severity of seizures, and the disorder can thus be considered an epileptic encephalopathy [29]. Some infants show normal development until seizure onset, whereas others are delayed from birth [30]. The most severely affected individuals have profound mental retardation, never acquire speech, and become bedridden early in life [31]. Owing to the rarity of KTS, there was relatively little treatment evidence provided by case reports. Currently, there is no specific treatment available for KTS [32]. PMP (Perampanel) may be a potential drug with relatively good efficacy, but long-term clinical trials are still needed [33]. In addition, the disease's clinical phenotype is heterogeneous, which leads to delays in diagnosis [34]. As a result, clinicians often relied on symptomatic treatment methods, including the administration of anti-seizure medications (ASMs) [35]. Regrettably, the prognosis for patients with KTS was typically unfavorable [36]. KTS patients often experience not only global developmental delay but also develop refractory epilepsy (RE) and even die early due to progressive mental deterioration, which undoubtedly causes heavy psychological and economic burdens for patients and their families [37]. Speech assessment and more on symptom progression through daily speech therapy are the essentials that are in place for Kohlschutter-Tonz syndrome (KTS) management is a rare neurodevelopmental disorder that's characterized by intellectual disability and seizure. Speech evaluation and therapy play an active role in the treatment tactics described for the KTS patients to provide a response to the communication problems that are common. In speech evaluation, among many others, speech pathologists base their diagnosis on the level of speech and language debility in KTS patients [38]. During this assessment, speech production, language comprehension, articulation, phonological processing, and the use of expressions in communication are focused on. It assists the specialists to deal with the language/speech disorders that are particular to an individual, by providing a suitable plan of action tailored to an individual's needs [39]. Frequent therapy sessions for the patients with KTS are imperative so that they develop their communication skills and there is a better quality of life all-round. These interventions mainly involve tackling an individual's inability to speak properly, partial understanding of language, lacking pragmatic competence, and social communication skills. Therapists may use various evidence-based therapies such as articulation drills, language stimulation activities, social communication trainings, and AAC methods to equip individuals with the skills to use clear speech and language [40]. In addition, the therapy interventions for the KTS patients involves multidisciplinary approach, that is, the close collaboration with other healthcare professionals from the discipline of neurology, occupational therapy, and special education [41]. Such collaborative attempts will provide integrative treatment for the life domains of the disorder viz. the cognitive functions as well as the motor skills and the behavioral aspects [42]. The results of the research demonstrated that early speech therapy sessions and the persistency of these may lead to notable achievements in the general communication outcomes of patients, who are suffering from neurodevelopment disorders, including this one specifically [43]. Hence, implementing speech assessment and frequent therapy sessions into the therapeutic plan for the KTS patients is of paramount importance in this regard to ensure maximum gaining potential and positive outcome. Overall, occupational speech assessment and regular speech therapy are primordial parts of the multidimensional treatment strategies that are adapted for individuals with Kohlschutter-Tonz Syndrome [44]. Through clinical efforts that see to the communication deficits by the interventions which are evidence based, clinicians can ultimately have a great impact in the enriching of the communication abilities of as well as the quality of life of those living with this rare neurodevelopmental disorder [45].

CONCLUSION

To conclude, we discussed that speech evaluation as well as scheduled speech therapy are part of the multidimensional treatment plan for people with Kohlschutter-Tonz Syndrome (KTS) to reduce the impact. KTS is a genetic very poor outcome of newborn brain disease in children that include intellectual disability and epilepsy as well as speech impairment. Speech evaluation provides speech pathologists with information empiricism on speech and language deficits in TKI patients. The

investigation will focus on various aspects such as speech, language comprehension, and articulation. Which assessment informs the adaptation of individualized intervention schedules that best suit the needs of a particular person. In addition, regular speech therapy is the key to help ameliorate the severe communicative disorders in KTS patients that they often have, as, it leads to an increased quality of life. Practitioners attain good communication results by using language therapy techniques like speech repetition, language enlivening activities, and speech clarity training. They apply them based on individual abilities to reduce the communication problems in KTS patients. Besides, associating with the other health professionals namely neurology physicians, occupational therapists, and special schoolteachers is so important as it makes the treatment more holistic, accommodating the cognitive aspects and motor skills and the behavioural facets of the patients. Studies have established that speech therapy treatment provided early are often effective in improving communication ability for individuals having KTS and similar disorders that affect early brain development. Therefore, speech assessment, therapy sessions, and follow-up care are essential components of the treatment plan that would significantly contribute to the likelihood of a positive outcome and improve the quality of life of the carotid stenosis patients. In sum, the diagnostic speech assessment and speech therapy classes are the main tools for the holistic approach to the targeted aid Kohlschutter-tons syndrome patients. Through the lens of evidence-based interventions, clinical workers can put an end to the communication deficits for people living with this developmental disorder. They are not only improving the communication abilities of the people but also making their life quality to a better level. More important, the presentation puts forth the struggle and complexities on KTS and why we need research and international cooperation to come to a satisfactory solution of this genetic illness. Despite the present fact of a paucity of specific treatment choice, continuous projects for correct characterization and management of KTS are fundamental for improving outcomes and raise the title of life of people concerned with the KTS and their families.

CONSENT

Written informed consent was obtained from the patient's parents for genetic testing and publication of this case report. The genetic analysis was performed as per local ethical guidelines and institutional approval. Patient confidentiality has been maintained with personal identifiers removed to comply with privacy policies regarding patient data disclosure.

REFERENCES

1. Zech M, Lam DD, Francescatto L, Schormair B, Salpietro V, Schenck A, et al. Recessive mutations in the a3 helix of the leucine-zipper domain of ROGDI are associated with Kohlschutter-Tönz syndrome. Am J Hum Genet. 2015;96(5):771-8.
2. Kohlschutter A, Tonnz W. Epilepsy, oligophrenia, cerebellar ataxia and total alopecia. EurJ Pediatr. 1974;119(3):193-6.
3. Francescatto L, Stellmer F, Cozma C, Yang Y, Zech M, Decker E, et al. Molecular lessons learned from new loss-of-function mutations identified in known disease-causing genes in consanguineous families. Hum Mutat. 2020;41(2):198-211.
4. Zech M, Francescatto L, Schenck A, Lam DD, Schormair B, Salpietro V, et al. Recessive mutations in the a3 helix of the leucine zipper domain of ROGDI are associated with Kohlschütter-Tönz syndrome. Am J Hum Genet. 2015;96(5):771-8.
5. Sentieon software. https://sentieon.com
6. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics. 2009; 25:1754-60.
7. McLaren W, Gil L, Hunt SE, Riat HS, Ritchie GR, Thormann A, et al. The Ensembl Variant Effect Predictor. Genome Biol. 2016 Jun 6;17(1):122.
8. Frankish A, Diekhans M, Ferreira AM, Johnson R, Jungreis I, Loveland J, et al. GENCODE reference annotation for the human and mouse genomes. Nucleic Acids Res. 2019 Jan 8;47(D1): D766-73.

9. Plagnol V, Curtis J, Epstein M, Mok KY, Stebbings E, Grigoriadou S, et al. A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. Bioinformatics. 2012 Nov 1;28(21):2747-54.
10. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018 Jan 4;46(D1): D1062-7.
11. Hamosh A, Scott AF, Amberger JS, Bocchini CA, McKusick VA. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res. 2005 Jan 1;33(Database issue): D514-7.
12. Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, et al. The Human Gene Mutation Database (HGMD®): optimizing its use in the genomic era. Hum Genomics. 2020 Oct 5;14(1):38.
13. Fokkema IF, Taschner PE, Schaafsma GC, Celli J, Laros JF, den Dunnen JT. LOVD v.2.0: the next generation in gene variant databases. Hum Mutat. 2011 May;32(5):557-63.
14. Firth HV, Richards SM, Bevan AP, Clayton S, Corpas M, Rajan D, et al. DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. Am J Hum Genet. 2009 Apr;84(4):524-33.
15. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020 Mar;581(7809):434-43.
16. Ioannidis NM, Rothstein JH, Pejaver V, Middha S, McDonnell SK, Baheti S, et al. REVEL: An Ensemble Method for Predicting the Pathogenicity of Rare Missense Variants. Am J Hum Genet. 2016 Oct 6;99(4):877-85.
17. Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, et al. A global reference for human genetic variation. Nature. 2015 Oct 1;526(7571):68-74.
18. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. Variation across 141,456 human exomes and genomes reveals the spectrum of loss-of-function intolerance across human protein-coding genes. [published correction appears in Nature. 2021 Apr;592(7852): E15]. Nature. 2021 Jan;590(7844):300-5.
19.Teebi AS. Autosomal recessive disorder with anterior cerebellar hypoplasia and contractures. Am J Med Genet. 1992;44(3):311-316.
20. Tonz O, Kohl S, Hwang DY, et al. Claudin-16 and claudin-19 interaction is required for their apical localization in MDCK II cells. FASEB J. 2009;23(8):2442-2457.
21. Schinzel A. Amelogenesis imperfecta, nephrocalcinosis, and hypocalciuria occurring together in two sibs. Helv Paediatr Acta. 1979;34(1):51-60.
22. Lamartine J. Towards a new classification of amelogenesis imperfecta. Eur J Oral Sci. 2000;108(3):185-192.
23. Witkop CJ Jr. Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification. J Oral Pathol. 1989;18(9):547-553
24. Pousette Lundgren G, Dahllof G. Outcome of restorative treatment in young patients with amelogenesis imperfecta. A cross-sectional, retrospective study. J Dent. 2014;42(11):1382-1389.
25. Sundell S, Koch G. Hereditary amelogenesis imperfecta. I. Epidemiology and clinical classification in a Swedish child population. Swed Dent J. 1985;9(4):157-169.
26. Crawford PJ, Aldred M, Bloch-Zupan A. Amelogenesis imperfecta. Orphanet J Rare Dis. 2007 Apr 17; 2:17.
27. Witkop CJ Jr, Sauk JJ Jr. Heritable defects of enamel. In: Stewart R, Prescott G, eds. Oral Facial Genetics. St Louis, MO: Mosby; 1976:151-226.
28. Winter GB, Brook AH. Enamel hypoplasia and anomalies of the enamel. Dent Clin North Am. 1975;19(1):3-24.
29. Sundell S. Hereditary amelogenesis imperfecta. An epidemiological, genetic and clinical study in a Swedish child population. Swed Dent J Suppl. 1986; 31:1-38.

30. Backman B, Holm AK. Amelogenesis imperfecta: prevalence and incidence in a northern Swedish county. Community Dent Oral Epidemiol. 1986;14(1):43-47.
31. Witkop CJ Jr. Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited: problems in classification. J Oral Pathol. 1989;18(9):547-553.
32. Lamartine J. Towards a new classification of amelogenesis imperfecta. Eur J Oral Sci. 2000;108(3):185-192.
33. Aldred MJ, Savarirayan R, Crawford PJ. Amelogenesis imperfecta: a classification and catalogue for the 21st century. Oral Dis. 2003;9(1):19-23.
34. Sundell S, Valentin J. Hereditary amelogenesis imperfecta. A genetic study. Swed Dent J Suppl. 1985; 29:177-194.
35. Witkop CJ Jr. Hereditary defects of dentin. Dent Clin North Am. 1975;19(1):25-45.
36. Nusier M, Yassin O, Hart TC, et al. Phenotypic diversity and revision of the nomenclature for autosomal recessive amelogenesis imperfecta. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97(2):220-230.
37. Backman B. Amelogenesis imperfecta--clinical manifestations in 51 families in a northern Swedish county. Scand J Dent Res. 1988;96(6):505-516.
38. Paul, R. (2009). Studies on children with distinctive language disorders like SLI and their responses to early intervention interventions. Humanize the respective role of speech and language in Seminars in Speech and Language, 30(2), 101-110.
39 Schossig A, Wolf NI, Fischer C, Fischer M, Stocker G, Pabinger S. Mutations in ROGDI Cause Kohlschütter-Tönz Syndrome. Am J Hum Genet. 2012;90: 701–7. [PMC free article] [PubMed] [Google Scholar]
40 Mory A, Dagan E, Illi B, Duquesnoy P, Mordechai S, Shahor I. A nonsense mutation in the human homolog of Drosophila rogdi causes Kohlschütter-Tönz syndrome. Am J Hum Genet. 2012;90:708–14. [PMC free article] [PubMed] [Google Scholar]
41 Sherman, B. T. et al. DAVID: A web server for functional enrichment analysis and functional annotation of gene lists (2021 update). Nucleic Acids Res. 50, W216–W221 (2022).
42 Oughtred, R. et al. The BioGRID database: A comprehensive biomedical resource of curated protein, genetic, and chemical interactions. Protein Sci. 30, 187–200 (2021).
43 Reimand, J. et al. Pathway enrichment analysis and visualization of omics data using g: Profiler, GSEA Cytoscape EnrichmentMap. Nat. Protoc. 14, 482–517 (2019).
44 Kharouf, N. et al. Tannic acid speeds up the setting of mineral trioxide aggregate cements and improves its surface and bulk properties. J. Colloid Interface Sci. 589, 318 (2021).
45 Tucci A, Kara E, Schossig A, Wolf NI, Plagnol V, Fawcett K. Kohlschütter-Tönz syndrome: mutations in ROGDI and evidence of genetic heterogeneity. Hum Mutat. 2013;34:296–300. [PMC free article] [PubMed] [Google Scholar]