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RESEARCH ARTICLE

A novel homozygous mutation in *SZT2* gene in Saudi family with developmental delay, macrocephaly and epilepsy

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Abstract

Epileptic encephalopathies are genetically heterogeneous disorders which leads to epilepsy and cause neurological disorders. Seizure threshold 2 (*SZT2*) gene located on chromosome 1p34.2 encodes protein mainly expressed predominantly in the parietal and frontal cortex and dorsal root ganglia in the brain. Previous studies in mice showed that mutation in this gene can confers low seizure threshold, enhance epileptogenesis and in human may leads to facial dysmorphism, intellectual disability, seizure and macrocephaly. Objective of this study was to find out novel gene or novel mutation related to the gene phenotype. We have identified a large consanguineous Saudi family segregating developmental delay, intellectual disability, epilepsy, high forehead and macrocephaly. Exome sequencing was performed in affected siblings of the family to study the novel mutation. Whole exome sequencing data analysis, confirmed by subsequent Sanger sequencing validation study. Our results showed a novel homozygous mutation (c.9368G>A) in a substitution of a conserved glycine residue into a glutamic acid in the exon 67 of *SZT2* gene. The mutation was ruled out in 100 unrelated healthy controls. The missense variant has not yet been reported as pathogenic in literature or variant databases. In conclusion, the here detected homozygous *SZT2* variant might be the causative mutation that further explain epilepsy and developmental delay in this Saudi family.

Keywords *SZT2* gene · Epilepsy · Intellectual disability · Saudi family

Introduction

The most complex biological system is the human brain (Kasperaviciute et al. 2010). Epilepsy is one of the abnormality that can affect different part of the brain. It was defined the epilepsies by recurrent seizures, which can cause motor, sensory, cognitive, psychic or autonomic disturbances (Steinlein 2004), World Health Organization (WHO) estimates that eight people per 1000 worldwide have this disease. The prevalence of epilepsy in developing countries is usually higher than undeveloped countries (Brunklaus et al. 2015).

Epilepsies can be classified in to three classes, idiopathic, cryptogenic, and symptomatic. Approximately 20–30% of epilepsies are caused by injuries in the central nervous system (CNS) or gray matter like trauma, CNS infection, bleed, stroke, cerebral palsy, metabolic insults, etc. These types of epilepsy are classified as symptomatic according to the International Classification of Epileptic Syndromes. While the remaining 70–80% of the cases are categorized as idiopathic or cryptogenic. The idiopathic epilepsies are of genetic origin while "cryptogenic," for syndromes presumed to be nongenetic cause for epilepsy (Ottman 1997). In the keep going decades a large amount of gene discoveries changed our perspectives of idiopathic infection and symptomatic epilepsy (Lee et al. 2015), more than 200 single gene disorders are known in which epilepsy is a more or less important part of the phenotype (Steinlein 2004). The Arab world is unique in terms of mixed ethnicity, varied religious practices and consanguineous marriages this make

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it difficult to find the cause of the disease (Nakajima et al. 2012). Recently, we identified a novel mutation in *PGAP2* gene causes developmental delay, intellectual disability (IDs), epilepsy in consanguineous Saudi family (Naseer et al. 2016).

The improvement in genetic analysis have led to the identification of large numbers of novel gene mutations that underlie infantile-onset epileptic encephalopathies. Previously, a mutagenesis screen specified a novel gene, *SZT2*, with no known protein role that has been linked to epileptogenesis in mice (Frankel et al. 2009). *SZT2* is highly conserved in animals, with highest conservation in the first third of the N terminus. Both mice and human *Szt2* are mainly expressed in the brain, predominantly in the parietal and frontal cortex as well as in dorsal root ganglia (Frankel et al. 2009; Toutzaris et al. 2010). Based on co-localization studies, human *SZT2* is localized to the peroxisomes (Toutzaris et al. 2010), this study also showed that *SZT2* expression is up regulated in cells resistant to oxidative stress, and that the protein provides a modest protective effect against oxidative stress. Moreover, the presence of a superoxide dismutase (SOD) motif in the *SZT2* protein, it was suggested that it likely functions by increasing SOD activity, but itself has no direct SOD activity (Toutzaris et al. 2010). Up to now, only two clinical record have identified children with recessive mutations in *SZT2* and varying clinical phenotypes. Recently, a study report showed a patients with epileptic encephalopathy with cognitive deficiencies, but normal MRI and no epilepsy (Venkatesan et al. 2016).

We aim to study genetics and molecular causes of inherited epilepsy in the Kingdom of Saudi Arabia. Our results showed that large consanguineous family suffering with developmental delay, IDs, poor hearing, epilepsy and marked macrocephaly. The whole exome sequencing revealed novel missense mutation in *SZT2* gene might be the underlying cause leading to epilepsy in this family.

Materials and methods

Sample collections

Samples from patients were collected following the appropriate local ethical protocols and guidelines from the Al-Aziziah Maternity & Children Hospital, Jeddah. Informed written consent was taken from all the participants according to the Helsinki declaration. The study was also approved the ethical committee of the Center of Excellence in Genomic Medicine Research, King Abdulaziz University, Jeddah. MRI and electroencephalography (EEG) were performed to exclude infection or trauma and to evaluate the severity and laterality of the disease.

Genomic DNA extraction

Genomic DNA was extracted from peripheral blood samples using a MegNA Pure 24 system (Roche Life Science, Mannheim, Germany). The detailed family pedigree was drawn after complete information form the family as shown in Fig. 1. The samples were prepared for exome sequencing according to an Agilent Sure Select Target Enrichment Kit Preparation guide (Agilent Santa Clara, CA, USA). The blood samples were collected from all five members of the family (two affected one normal individual and two parents) and one hundred unrelated healthy people as controls from Saudi origin. Both the affected individuals underwent medical examination at Al-Aziziah Maternity & Children Hospital, Jeddah.

Patient 1 (IV-1)

Proband (IV-1) is a female currently at the age of 8 year and visited our clinic first the time when she was 6 years old (Fig. 2a). She was the born of Saudi parents who were first cousins, and was delivered by cesarean section due to macrosomia the detailed pedigree is shown in Fig. 1. Her birth weight was 3.6 kg, height 51 cm and head circumference (HC) 37 cm. Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score was 9 at 1 min and 10 at 5 min. She was discharge with no complaints. At 11 months of age she was seen at pediatric consultation because hypotonia, developmental delay, IDs, floppiness and delayed milestones. Her HC was recorded as 49 cm above the 95th percentile, height 75 cm 50th percentile, and weight 9.2 kg in the 10th percentile for her age. She was seen again at 5 years of age her HC was 51.5 cm above 95th percentile, Height 87 cm in the 25th percentile and her weight 12 kg in the 5th percentile. At 3 years of age, she was not able to walk or stand or sit without support and cannot even crawl. Her language was practically absent and limited to guttural sounds without words. There was a history of seizures or abnormal movements. She did not have dysmorphic features or skin

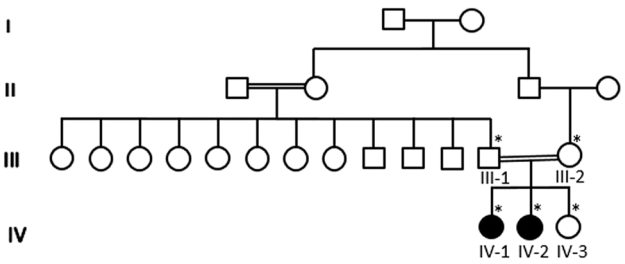

Fig. 1 A consanguineous family from Saudi Arabia showing the disease phenotype segregating in an autosomal recessive manner. The samples marked with asterisks was available for genetic testing

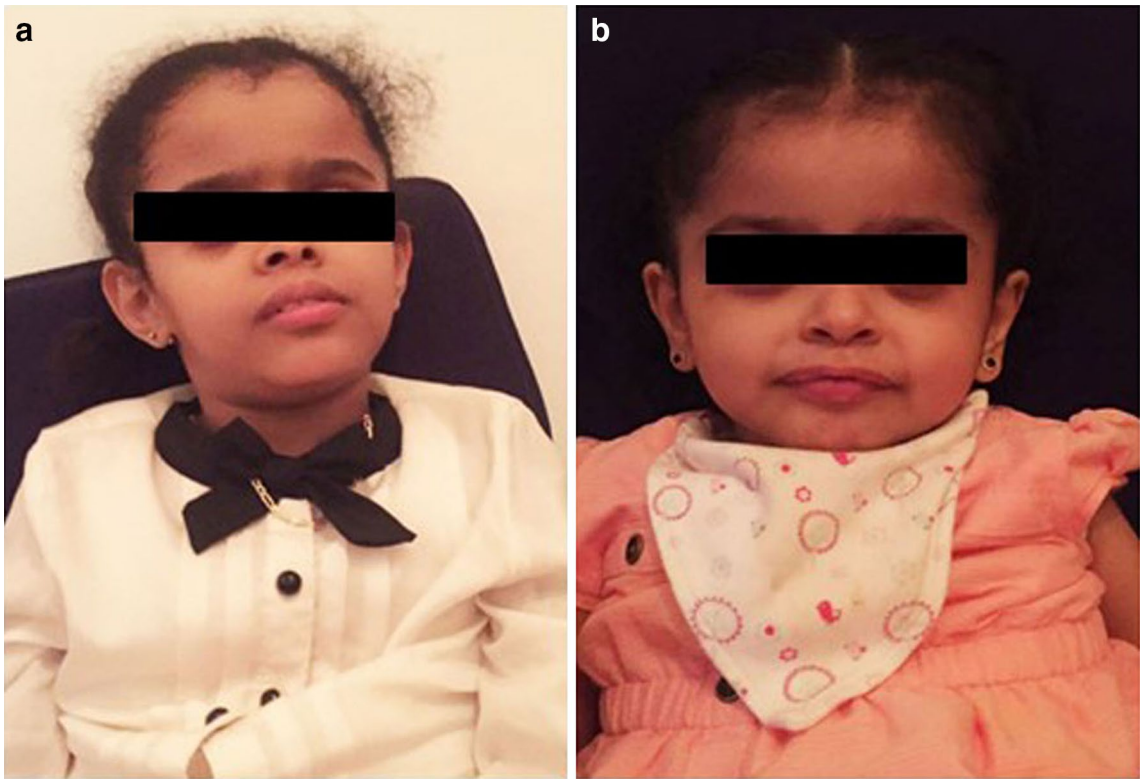

Fig. 2 Photographic representation of the affected individuals: **a** IV-1 and **b** IV-2 proband of the family. Informed written consent has been obtained from the patient's parents for presentation of data and photographic representation in the manuscript

Table 1 Detailed clinical information of the patients

Clinical information	Patient 1 (IV-1)	Patient 2 (IV-2)
Sex	Female	Female
Age	8 years	5 years
Delivery	Cesarean section	Cesarean section
Birth weight	3.6 kg	3.5 kg
Height at birth	51 cm	52 cm
Head circumference at birth	37 cm	36 cm
APGAR score	9 at 1 min and 10 at 5 min	8 at 1 min and 10 at 5 min
Phenotypic features	Developmental delay, hypotonia, floppiness and delayed milestones	Developmental delay, hypotonia, floppiness and delayed milestones
Head circumference now	51.5 cm	51 cm
Height	87 cm	90 cm
Current weight	12 kg	11.5 kg
Language	Practically absent and limited to guttural sounds	Absent
Seizures	Yes	Yes
Dysmorphic features	No	No
Skin stigmata	No	No
Cranial nerves	Normal	Normal
Cardiopulmonary	Normal	Normal
Abdominal masses	No abdominal masses or organomegaly	No abdominal masses or organomegaly

stigmata. Cranial nerves were normal, cardiopulmonary normal, and no abdominal masses or organomegaly as shown in Table 1. Routine laboratory complete blood count (CBC), thyroid hormone, liver enzymes, creatinine, ammonia, lactic acid were normal. Tandem Mass Spectrophotometry was normal Chest X-rays, abdominal ultrasound was normal. Brain MRI showed prominent extra axial cerebrospinal fluid (CSF) space with wide Sylvian fissure, no abnormal signal intensity, no ventriculomegaly, normal corpus callosum, normal posterior fossa and cerebellum.

Patient 2 (IV-2)

Proband (IV-2) a female of 5 year old and she visited the clinic at the age of 3 years old the first time in the Al-Aziziah Maternity & Children Hospital, Jeddah (Fig. 2b). She was also born by cesarean section due to macrosomia. Her birth weight was 3.5 kg, height 52 cm and HC 36 cm. APGAR score was 8 at 1 min and 10 at 5 min. She was also discharge with no complaints after delivery. She was also seen at pediatric consultation because developmental delay, hypotonia, floppiness and delayed milestones similar as to her elder sister. Her HC was recorded as 48 cm above the 95th percentile, height 73 cm 50th percentile, and weight 8.5 kg in the 10th percentile for her age. She was seen again at 2 years of age her HC was 50.5 cm above 95th percentile, Height 85 cm in the 25th percentile and her weight 10 kg in the 5th percentile. She was not able to walk or stand or sit without support until at the age of 3 years. Her language was practically absent and limited to guttural sounds without words. There was a history of seizures or abnormal movements similar to her sister. At examination her HC was 51 cm in the 95th percentile, Height was 90 cm in the 10th percentile and her weight 11.5 kg below the 5th percentile. She also did not have dysmorphic features or skin stigmata. Cranial nerves were normal, cardiopulmonary normal, and no abdominal masses or organomegaly as shown in Table 1. Routine laboratory CBC, thyroid hormone, liver enzymes, creatinine, ammonia, lactic acid were normal. Tandem mass spectrophotometry was normal Chest X-rays, abdominal ultrasound was normal. Brain MRI showed prominent extra axial CSF space with wide Sylvian fissure, no abnormal signal intensity, no ventriculomegaly, normal corpus callosum, normal posterior fossa and cerebellum were scene. Detailed affected and normal offspring in this family are shown in pedigree (Fig. 1).

EEG testing

EEG was done for proband IV-1 was 8 years old and proband IV-2 was 5 year old girls. Epilepsy presented with seizures in Dr. Bakhsh Hospital Al-Sharafia, Jeddah. Asleep EEG was recorded in order to understand the epilepsy and seizure and excessive fast activity generalized slowing over C4, T4 and O2 in both of the proband while intermittent multifocal spikes more on the right side of the proband IV-1 as compared to the IV-2.

Exome sequencing and bioinformatics analysis

To identify the underlying pathogenic mutation behind this disease phenotype we did whole exome sequencing using Illumina HiSeq 2000/2500. The samples were prepared according to an Agilent SureSelect Target Enrichment Kit preparation guide (SureSelect_v6 Agilent USA). The libraries were sequenced with Illumina HiSeq 2000/2500 sequencer. These variants were filtered based on quality, frequency, genomic position, protein effect, pathogenicity and previous associations with the phenotype. Various bioinformatics analyses were carried to identify causative variant co-segregating with the *SZT2* phenotype in an autosomal recessive fashion using Lasergene Genomic Suite v. 12 (DNASTAR, Madison, WI, USA). Raw data FASTQ files were aligned using the BWA Aligner (http://bio-bwa.sourceforge.net/) and were aligned to hg19 (NCBI build GRCh37) using SeqMan NGen 12 (DNASTAR). ArrayStar v. 12 (Rockville, MD, USA) was used to label variant alleles based on dbSNP 142. Copy number variation and insertion/deletion (InDel) detection were performed using SAMTOOLS (http://samtools.sourceforge.net/). The sequence reads were mapped against the hg19 human reference sequence (http://genome.ucsc.edu/) and compared against sequences in the dbSNP (http://www.ncbi.nlm.nih.gov/snp/) and the 1000 Genomes Project databases (http://www.1000genomes.org/data). To reduce the pool of potential variants, we applied the following criteria. (1) Candidate variants were expected to follow an autosomal recessive inheritance pattern (homozygous or compound heterozygous state) given the reported positive family history. Homozygous variants were of primary interest based on the positive consanguinity. (2) Variants showing a minor allele frequency > 0.05 in the 1000 Human Genome database (http://www.1000genomes.org/) were excluded. (3) Homozygous variants in our inhouse exome sequence data obtained were excluded. (4) Synonymous and deep intronic variants other than those present at splice junctions were excluded. (5) Thereafter rare, potentially harmful variants present in those genes in (compound) heterozygous state (or possibly de novo) state were further considered. However, this approach did not yield a plausible candidate. The analysis was then expanded to all genes, whereby we firstly focused on potentially harmful homozygous variants and then moved on to potential candidates in (compound) heterozygous state. After applying these criteria we find a rare homozygous variants within the protein coding regions of all genes that have previously been

associated with one of the symptoms provided yielded one plausible candidate is the *SZT2* gene.

Sanger sequencing

SZT2 gene were amplified by polymerase chain reaction (PCR). Purified PCR products were subjected to cycle sequencing reactions by using BigDye Terminator V3.1 Cycle Sequencing kit to detect any mutation. To confirm the mutation in patients and family, we did Sanger sequencing using Applied Biosystems 3500 (CA, USA) Sequencer. Further to confirm the mutation as pathogenic, we also sequenced this DNA variant in unrelated 100 control people.

Results

EEG report

Asleep EEG record revealed a background of predominately beta wave rhythm. Paroxysmal epileptic discharge noted primarily on the right central hemispheres in both the affected individuals proband IV-1 and IV-2.

Identification of a homozygous mutation in *SZT2* gene

Whole exome sequencing of the index patient was done using Illumina HiSeq 2000/2500. The resulting variant call format (VCF) file contains 86,390 variants. These variants are filtered based on quality, genomic position, frequency, protein effect, pathogenicity and previous associations with the phenotype. On average, 94% of bases had a phred score > 20; the total number of bases in the reads was 10.5 Gb; and mean depth of the target region was 89. The resulting VCF file contains 86,390 variants those met quality control criteria (minimum Q call > 20, minimum depth > 10) of these, 13,820 were missense, silent, nonsense, or splice variants. These variants were filtered based on quality, frequency, genomic position, protein effect, pathogenicity and previous associations with the phenotype. After filtering out those that did not show a recessive mode of inheritance and those with a minor allele frequency < 0.05 based on the 1000 Human Genome database, 120 variants remained.

A screen of homozygous variants resulting in an amino acid change and those that were not present in our in-house exome sequence data of an unrelated healthy population (n = 18) yielded a novel homozygous mutation c.9368G>A results in a substitution of a conserved glycine residue into a glutamic acid in the exon 67 of *SZT2* gene. Subsequently, homozygous variants in genes were considered. This yielded a homozygous missense variant in the *SZT2* gene. Whole exome sequencing revealed pathogenic mutation in *SZT2* gene where G at position 9368 replaced by A resultantly amino acid glycine residue into a glutamic acid in the exon 67 showed a novel homozygous mutation c.9368G>A in affected members of the family as shown in Table 2. Furthermore, in the Greater Middle East variome minor allele frequency was 0.00 in the database. Moreover, PolyPhen 0.7, SIFT 0.12, PhyloP (phyloP46way_placental) and MutationTester (2.0) predicted this variation as disease causing mutation. This mutations was absent in the Human Gene Mutation database (HGMD, http://www.hgmd.cf.ac.uk/) and Online Mendelian Inheritance in Man (MIM/OMIM). 1000 genome (http://www.internationalgenome.org/) and The Exome Aggregation Consortium (ExAc) (Version 0.3.1) (http://exac.broadinstitute.org/) data base.

Sanger sequencing

Our results showed a novel homozygous c.9368G>A in both affected IV-1, and IV-2 proband whereas the parent's III-1, III-2 and one of the normal individual IV-3 were heterozygous at this position. The mutation found results in a substitution of a conserved glycine residue into a glutamic acid in the exon 67 of *SZT2* gene in the affected members of the family as shown in (Fig. 3). This mutation further validated in 100 unrelated healthy persons, but no one has this sequence variation. The parents of the affected members were heterozygous, which also confirms the autosomal recessive mode of inheritance.

Table 2 Pathogenic *SZT2* mutations reported until today

Nucleotide change	Amino acid change	Zygosity	Origin	Reference
c.73C>T	p.Arg25Ter	Homozygous	Iraqi Jewish	Basel-Vanagaite et al. (2013)
c.2092C>T(M) c.1496G-T(F)	p.Gln698Ter p.Ser499Ile	Compound heterozygous	Spanish	Basel-Vanagaite et al. (2013)
3-bp deletion (c.4202_4204delTTC)	p.Phe1401del	Homozygous	European American	Falcone et al. (2013)
c.3509_3512delCAGA(F) c.9703C>T(M)	p.T1170RfsX22 p.R3235X	Compound heterozygous	Not known	Venkatesan et al. (2016)
c. 9368G>A	p.Gly3123Glu	Homozygous	Saudi Arabia	Present study

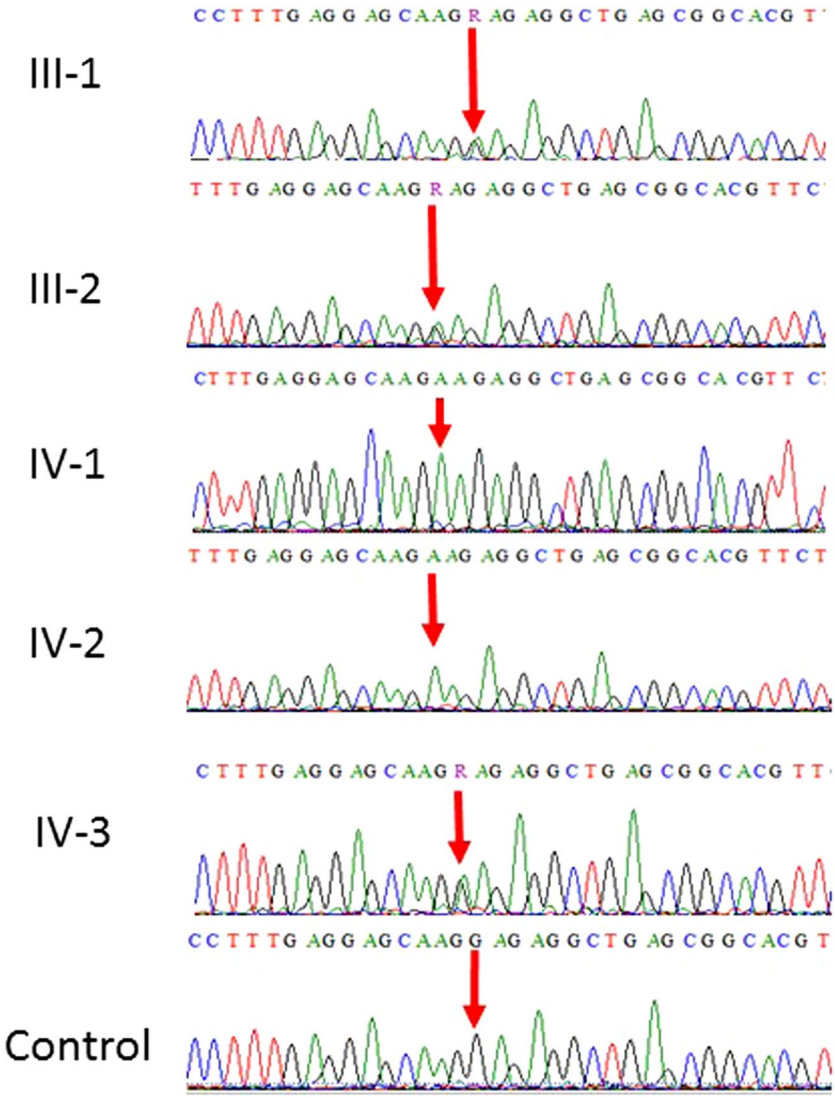

Fig. 3 Sanger sequence analysis: **a** and **b** (III-1 and III-2) are normal parents and normal female IV-3 showing G and A in heterozygous state, while (IV-1 and IV-2) are affected children showing only homozygous A in exon 67 of *SZT2* gene

Discussion

SZT2 is a previously identified gene that cause low seizure threshold and enhance epileptogenesis in mice when mutated (Frankel et al. 2009). Recessive mutations in *SZT2* have been associated with a form of early-infantile epileptic encephalopathy (EIEE) (Venkatesan et al. 2016; Basel-Vanagaite et al. 2013) and in another study with IDs without epilepsy and normal MRI (Falcone et al. 2013).

Previously, a homozygous nonsense mutation in *SZT2* and a nonsense mutation together with an exonic splice-site mutation in compound heterozygous state, as the cause of EIEE in two unrelated children was reported by (Basel-Vanagaite et al. 2013). These children presented with refractory epilepsy, severe developmental delay, absence of developmental milestones, and facial dysmorphic features (high forehead, down slanting palpebral fissures, ptosis, arched and laterally extended eyebrows). One of both children also presented with congenital heart defects including a thick mitral valve, mild hypertrophy of the intraventricular septum and mild aortic insufficiency. In addition, brain MRI showed a short and thick corpus callosum and persistent cavum septum pellucidum in both children. The study suggested an important role for *SZT2* in eliptogenesis and in human brain development (Basel-Vanagaite et al. 2013).

Recently, a frame shift and a nonsense mutation in *SZT2* present in compound heterozygous state, in a patient with intractable epilepsy (onset at 2 months of age), facial dysmorphisms (macrocephaly, high forehead, and downslanted palpebral fissures) developmental delay, ID and abnormal MRI findings was reported (Venkatesan et al. 2016). Two additional variants in *SZT2* have been identified in a girl presenting with severe epileptic encephalopathy, severe developmental delay, failure to thrive, delayed myelination, hypotonia, choreoathethosis, macrocephaly, absent reflexes, underdeveloped macula, recurrent, severe

pancreatitis, recurrent respiratory illness, poor dentition, intermittent rashes and alopecia. The variants c.5495delC (p.Ala1832fs) and c.6916G>A (p.Gly2306Arg) were shown to be present in compound heterozygous state. This case study has however not been published in a peer reviewed journal (see http://files.eventsential.org/d9c6bbbd-46a7-4784-83ee-ecad8eb1ad1e/event-240/57178686-Murphy.pdf).

Besides the association of *SZT2* with EIEE phenotypes, a homozygous in frame deletion in *SZT2* has been reported in three brothers with IDs, motor and/or speech delay and without epilepsy or brain abnormalities. The patients also had macrocephaly, but since the unaffected father was also macrocephalic, it is not clear whether this was linked to the *SZT2* variant. The detected homozygous c.4202_4204delTTC deletion was shown to segregate with ID and was present within a 19 MB autozygous region on chromosome 1 shared by three siblings. No functional studies were performed (Falcone et al. 2013). Based on the published pathogenic variants in *SZT2* and the associated phenotypes, clinical variability in disease expression is possible. The severity of *SZT2*-related phenotypes may depend on the residual activity of the protein which in turn depends on the specific pathogenic variant in *SZT2* (complete loss of function for truncating variants versus some residual activity for the in frame deletion variant). Furthermore, our patients showed macrocephaly that is the characteristic for *SZT2* mutations and macrocephaly has been observed in some patients. The missense variant detected in this study has not yet been reported as pathogenic in literature or variant databases. It results in a substitution of a conserved glycine residue into a glutamic acid. Missense mutations within *SZT2*, in contrast to the more severe nonsense and splice site mutations were described (Venkatesan et al. 2016; Basel-Vanagaite et al. 2013), might lead to variable disease presentation. Further research will be necessary to establish the clinical consequence of this variant. The variant was tested for likely pathogenic effect through in silico tools like Mutation Taster (Schwarz et al. 2014), SIFT and Polyphen, results showed the mutation found in this study was predicted as "disease causing" with high pathogenicity scores.

In conclusion, the here detected homozygous *SZT2* variant might explain epilepsy and developmental delay in these patient. For the first time, we find the novel missense mutation in *STZ2* gene in Saudi Arabia. Further study should be conducted with a large number of patients to get clear picture of epilepsy in Saudi Arabia. These findings can help to improve the clinical management of individual cases in lowering the burden of epilepsy in Saudi Arabia. Therefore, in this study we concluded that mutations in *SZT2* may cause a severe type of autosomal recessive infantile encephalopathy with seizures and distinct neuroradiological anomalies.

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Compliance with ethical standards

Conflict of interest All authors (1) Muhammad Imran Naseer, (2) Mohammad Khalid Alwasiyah, (3) Angham Abdulrahman Abdulkareem, (4) Rayan Abdullah Bajammal, (5) Carlos Trujillo, (6) Muhammad Abu-Elmagd, (7) Mohammad Alam Jafri, (8) Adeel G. Chaudhary, (9) Mohammad H. Al-Qahtani declare that they have no conflict of interest.

Ethical approval This study was approved by the Institutional Review Board Committees at CEGMR King Abdulaziz University Jeddah Saudi Arabia.

Informed consent Written informed consent was obtained from all study participants from this family.

References

Basel-Vanagaite L, Hershkovitz T, Heyman E et al (2013) SZT2 mutations cause infantile encephalopathy with epilepsy and dysmorphic corpus callosum. Am J Hum Genet 93:524–529

Brunklaus A, Ellis R, Stewart H, Aylett S et al (2015) Homozygous mutations in the SCN1A gene associated with genetic epilepsy with febrile seizures plus and Dravet syndrome in 2 families. Eur J Paediatr Neurol 19:484–488

Falcone M, Yariz KO, Ross DB, Foster J, Menendez I, Tekin M (2013) An amino acid deletion in SZT2 in a family with non-syndromic intellectual disability. PLoS ONE 8(12):e82810

Frankel W, Yang Y, Mahaffey C, Beyer B, O'Brien T (2009) Szt2, a novel gene for seizure threshold in mice. Genes Brain Behav 8(5):568–576

Kasperaviciute D, Catarino C, Heinze E, Depondt C et al (2010) Common genetic variation and susceptibility to partial epilepsies a genome-wide association study. Brain 133:2136–2147

Lee H, Chi C, Tsai C, Chen C, Wang C (2015) Electroencephalographic features of patients with SCN1A-positive Dravet syndrome. Brain Dev 37:599–611

Nakajima K, Yin X, Takei Y, Seog D, Homma N, Hirokawa N (2012) Molecular motor KIF5A is essential for GABAA receptor transport, and KIF5A deletion causes epilepsy. Neuron 76:945–961

Naseer MI, Rasool M, Jan MM, Chaudhary AG et al (2016) A novel mutation in PGAP2 gene causes developmental delay, intellectual disability, epilepsy and microcephaly in consanguineous Saudi family. J Neurol Sci 15:121–125

Ottman R (1997) Genetic epidemiology of epilepsy. Epidemiol Rev 19:120–128

Schwarz JM, Cooper DN, Schuelke M, Seelow D (2014) MutationTaster2: mutation prediction for the deep-sequencing age. Nat Methods 11:361–362

Steinlein O (2004) Genetic mechanisms that underlie epilepsy. Nat Rev Neurosci 5:400–408

Toutzaris D, Lewerenz J, Albrecht P et al (2010) A novel giant peroxisomal superoxide dismutase motif-containing protein. Free Radic Biol Med 48:811–820

Venkatesan C, Angle B, Millichap JJ (2016) Early-life epileptic encephalopathy secondary to *SZT2* pathogenic recessive variants. Epileptic Disord 18:195–200