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SHORT COMMUNICATION

EPG5 c.1007A > G mutation in a sibling pair with rapidly progressing Vici syndrome

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Abstract

We report on a sibling pair with the *EPG5* c.1007A > G mutation who developed a severe form of Vici syndrome and died in infancy. The c.1007A > G (p.Gln336Arg) mutation, affecting the penultimate nucleotide and the splicing of exon 2 is the most common mutation of *EPG5* and is typically associated with a less devastating prognosis: cardiomyopathy and cataract are less frequent consequences and the median survival time is 78 months compared to an overall median survival of 42 months. The less severe course related to c.1007A > G was formerly explained by the preserved canonical splicing in 25% of the transcripts. In contrast, we found the messenger RNA encoded by the c.1007A > G allele to be absent, explaining the severe course of the disease. This family provides another example of phenotypic variability related to a differential splicing.

KEYWORDS

differential splicing, Gln336Arg, phenotype variability, Vici syndrome

1 | INTRODUCTION

Carlo Dionisi-Vici described two brothers with agenesis of the corpus callosum, combined immunodeficiency, bilateral cataract, and hypopigmentation in 1988 (Dionisi-Vici et al., 1988). In addition to these phenotypic features, cardiomyopathy, developmental delay, microcephaly, and failure to thrive were described as typical consequences (Byrne et al., 2016c; Chiyonobu et al., 2002; del Campo et al., 1999). Since the first description, more than 40 families have been published with Vici syndrome (VICIS), who were compatible with an autosomal recessive transmission and have extended the variable clinical spectrum with myopathy, epilepsy, elevated aminotransferases, thymus aplasia, thrombocytopenic purpura, sensorineural hearing loss, and renal tubular acidosis (Aggarwal, Tandon, Bhowmik, & Dalal, 2018; Al-Owain et al., 2010; Alzahrani, Alghamdi, & Waggass, 2018; Balasubramaniam et al., 2018; Byrne et al., 2016c; Chiyonobu et al., 2002; Cullup et al., 2013; del Campo et al., 1999; Demiral, Sen, Esener, Ceylaner, & Tekedereli, 2018; El-Kersh, Jungbluth, Gringras, & Senthilvel, 2015; Hedberg-Oldfors, Darin, & Oldfors, 2017; Hori et al., 2017; Huenerberg et al., 2016; Maillard et al., 2017; McClelland et al., 2010; Miyata et al., 2007; Ozkale, Erol, Gümüs, Ozkale, & Alehan, 2012; Rogers, Aufmuth, & Monesson, 2011; Said, Soler, & Sewry, 2012; Shimada et al., 2018; Waldrop et al., 2018). The prognosis was found to be poor with a median survival of 42 months (Byrne, Dionisi-Vici, Smith, Gautel, & Jungbluth, 2016b). There is, however, a significant difference in the severity and the overall survival (Byrne et al., 2016c; Hori et al., 2017).

Mutations of *EPG5* (18q12.3) were identified in 2013 by whole exome sequencing (Cullup et al., 2013). The encoded protein, ectopic P-granules autophagy protein 5 is a Rab7

effector mediating the fusion specificity between autophagosomes and lysosomes (Cullup et al., 2013; Hori et al., 2017; Wang et al., 2016). Loss of *EPG5* results in the accumulation of autophagic cargo in autophagosomes (Byrne et al., 2016c; Ehmke et al., 2014).

Most of the *EPG5* mutations are null (Byrne et al., 2016c). Patients with biallelic loss-of-function mutations typically develop severe cardiomyopathy and immunodeficiency, leading to a markedly reduced life expectancy (Supplemental Table 1; Byrne et al., 2016b).

The most common *EPG5* mutation, reported in four unrelated families with Caucasian or Ashkenazi origin, is the c.1007A > G mutation (rs201757275) with an allele frequency of 2.85×10^{-5} in Europe (http://gnomad.broadinstitute.org) (Byrne et al., 2016c). It causes an amino acid substitution (p.Gln336Arg) and, affecting the penultimate nucleotide of the second exon, leads to aberrant splicing and messenger RNA (mRNA) decay in 75% and 50% of the transcripts (Byrne, Cullup, Fanto, Gautel, & Jungbluth, 2016a; Kane et al., 2016). The preserved canonical splicing in 25% of the transcripts allows the phenotype to be generally milder with a median survival time of 78 months. Accordingly, none of the four previously reported children with c.1007A > G developed severe cardiomyopathy and only two of them developed cataract (Supplemental Table 1; Byrne et al., 2016c).

Here we present two siblings with the c.1007A > G mutation who presented with an unexpectedly severe phenotype and died in infancy. We found all mRNA expressed from the c.1007A > G allele to be decayed, emphasizing the interfamiliar variability of splicing and the potential severity of the c.1007A > G mutation.

The index case was the third child of a nonconsanguineous Hungarian couple (Figure 1). The first child was born prematurely at the 31st gestational week with a normal length, weight, and head circumference. On examination, she had pale skin throughout her body and fair, sparse hair. Fundoscopy described stage I retinopathy of prematurity. Cranial ultrasound scan showed agenesis of the corpus callosum and cavum septum pellucidi. She presented with multiple episodes of aspirations, pneumonias, and a rotavirus gastroenteritis, and was diagnosed with generalized hypotonia, gastroesophageal reflux disease, and bilateral cataract by the age of 2 months. She did not acquire social smile throughout her life, failed to fix and follow at 3 months of age, and brainstem auditory-evoked responses supported the diagnosis of sensorineural hearing loss. At 5 months of age, she developed cardiomegaly with a cardiothoracic ratio of 0.75. Echocardiography showed bicuspid aortic valve and dilated cardiomyopathy with a progressive left ventricular dilatation (left ventricular end diastolic and end systolic diameter *z*-scores of 3.1 were 5.8, respectively), interventricular septal hypokinesis, and depressed ventricular function with a fractional shortening of 17%. She deteriorated quickly despite the combined therapy of digoxin, dopamine, dobutamine, furosemide, and captopril. Progressive failure to thrive resulted in severe

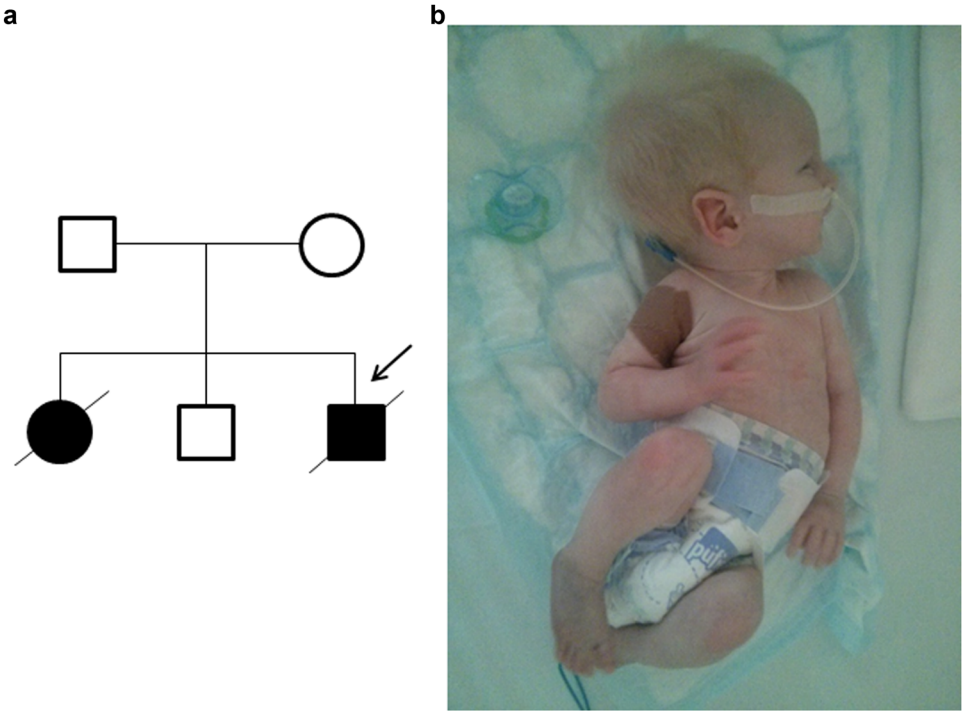

FIGURE 1 Pedigree (a) and phenotype (b) of the index patient. Note the oculocutan hypopigmentation, low set ears, and syndactyly of the second and third toes (b). Feeding difficulties necessitated nasogastric tube feeding [Colour figure can be viewed at wileyonlinelibrary.com]

hypotrophy, her weight dropped below the 0.4th centile at 6 months of age, when she died as a result of cardiac failure.

The second child is a healthy male adolescent.

The third child was a male, born 15 years after the first child from an uneventful pregnancy at term, with a normal weight, length, and head circumference (50th, 75th and 50th centiles, respectively). Physical examination revealed marked generalized oculocutan hypopigmentation, syndactyly of the 2nd and 3rd toes, low set ears, and severe hypotonia (Figure 1). Fundus examination revealed hypopigmentation. He developed apneas as a result of paroxysmal seizure activity as shown by an electroencephalogram. His seizures were resistant to a combined antiepileptic therapy of phenobarbital and phenytoin. Brain magnetic resonance imaging was consistent with VICIS showing cerebellar and brainstem hypoplasia, agenesis of the corpus callosum, dilated lateral ventricles, and small hippocampi. Routine laboratory investigations showed increased serum aspartate aminotransferase (111 U/L), alanine aminotransferase (124 U/L), lactate dehydrogenase (870 U/L), and creatine kinase and (841 U/L). He was treated for multiple septic episodes secondary to *Candida albicans*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* infections after the age of 2 weeks. The infections necessitated combined antibiotic treatment (including fluconazole for *C. albicans*, piperacillin/tazobactam for *P. aeruginosa*, and trimethoprim/sulfamethoxazole for *S. maltophilia*) and intravenous immunoglobulin supplementation. Recurrent unexplained fevers were common. Immunological workup showed normal T-cell subtype count, slightly elevated IgA (0.2 g/L), IgM (0.5 g/L), and low IgG (4.3 g/L) at 6 weeks of age. He was also diagnosed with a moderate dilated cardiomyopathy at 1 month of age with an ejection fraction of 37%, a grade II mitral and a grade I tricuspid regurgitation, and a left ventricular overload. He was started on furosemide and was followed up by a pediatric cardiologist in every second week. Severe gastroesophageal reflux disease necessitated an elective Nissen fundoplication and gastrotube insertion. Muscle biopsy confirmed marked variability in fiber size, centralized nuclei, and numerous large vacuoles on light microscopy.

At 6 weeks of age, he was diagnosed with cataract and secondary microcephaly (<9th centile), generalized muscle hypotonia, severe hypotrophy, and thoracolumbar kyphoscoliosis. Neurodevelopmental examination suggested sensorineural hearing loss. After establishing the diagnosis of Vici syndrome, the unfavorable prognosis was discussed with the family. The parents participated in a basic life support course and decided to take their child home when he was stable and well. Sorrowfully, 3 days later, he was readmitted for a new-onset sepsis. Repeated blood, urine, and cerebrospinal fluid cultures were negative. Despite the treatment with multiple combinations of broad-spectrum antibiotics (including piperacillin/tazobactam, meropenem, vancomycin, trimethoprim/sulfamethoxazole, fluconazole, and ceftriaxone) and intravenous immunoglobulins, he died 2 weeks later at the age of 3 months because of an overwhelming sepsis. Genetic counseling was provided to the parents.

2 | MATERIALS AND METHODS

Genomic DNA was extracted based on proteinase K digestion followed by high-sodium chloride treatment to precipitate proteins. The coding exons and the splicing junctions of *EPG5* (NM_020964) were Sanger sequenced in the Genetics Department of Guy's and St Thomas' Hospital, London, using primers as described previously (Cullup et al., 2013). Parental samples were Sanger sequenced to confirm transheterozygosity.

Total RNA was extracted from parental leukocytes with Macherey–Nagel NucleoSpin RNA Blood kit. No RNA was available from the affected child. The RNA samples were reverse-transcribed using the Thermo Fisher Maxima First Strand reverse transcription kit.

Parental complementary DNAs (cDNAs) were Sanger sequenced using MyTaq HS Mix (Bioline, London, UK). The primers TTCATGGCTGGAAAATGTTG (forward), GCACGGATACCAATTTCTGC (reverse), and ACCGGAGTCTGCTCTCATCT (forward), GGGGGTGATCAGAAGGTGTG (reverse) were used to amplify the regions encompassing the c.1007A > G maternal and the c.3768delA paternal mutations, respectively.

The amount of the c.1007A > G maternal mRNA was studied by quantitative polymerase chain reaction (qPCR) of cDNA with allele-specific primers: GAGGAACAAATGTCTGTACA (wild-type forward), GAGGAACAAATGTCTGTACG (c.1007A > G forward), and AAGAATGAAGGGCCAGGGTC (reverse). The initial denaturation (95°C for 5 min) was followed by 40 cycles of amplification (95°C for 5 s, 60°C for 5 s, 72°C for 7 s). The specificity of the c.1007A > G forward primer was validated with maternal genomic DNA (Supplemental Figure 1). Dilution series of a control cDNA was used to calculate the efficiency of the qPCR (Supplemental Figure 2). The qPCR was carried out on a LightCycler 480 system (Roche Diagnostics, Mannheim, Germany) with LightCycler 480 SYBR Green I Master enzyme mix (Roche Diagnostics).

To detect the splice isoforms encoded by the c.1007A > G allele, reverse transcription quantitative multiplex PCR of short fluorescent fragments (RT-QMPSF) was developed using the primers 2F_QMPSF: AGCATGGCTCATCAAGACAG and 3R_QMPSF: AGCTCCACCAGTGCATTTTC with universal tags (Carrington, Varshney, Burgess, & Sood, 2015). Briefly, a short cDNA sequence (275 bp) encompassing exons 2 and 3 was amplified with MyTaq HS Mix (Bioline) with the following conditions: the initial denaturation (95°C for 2 min) was followed by 30 cycles

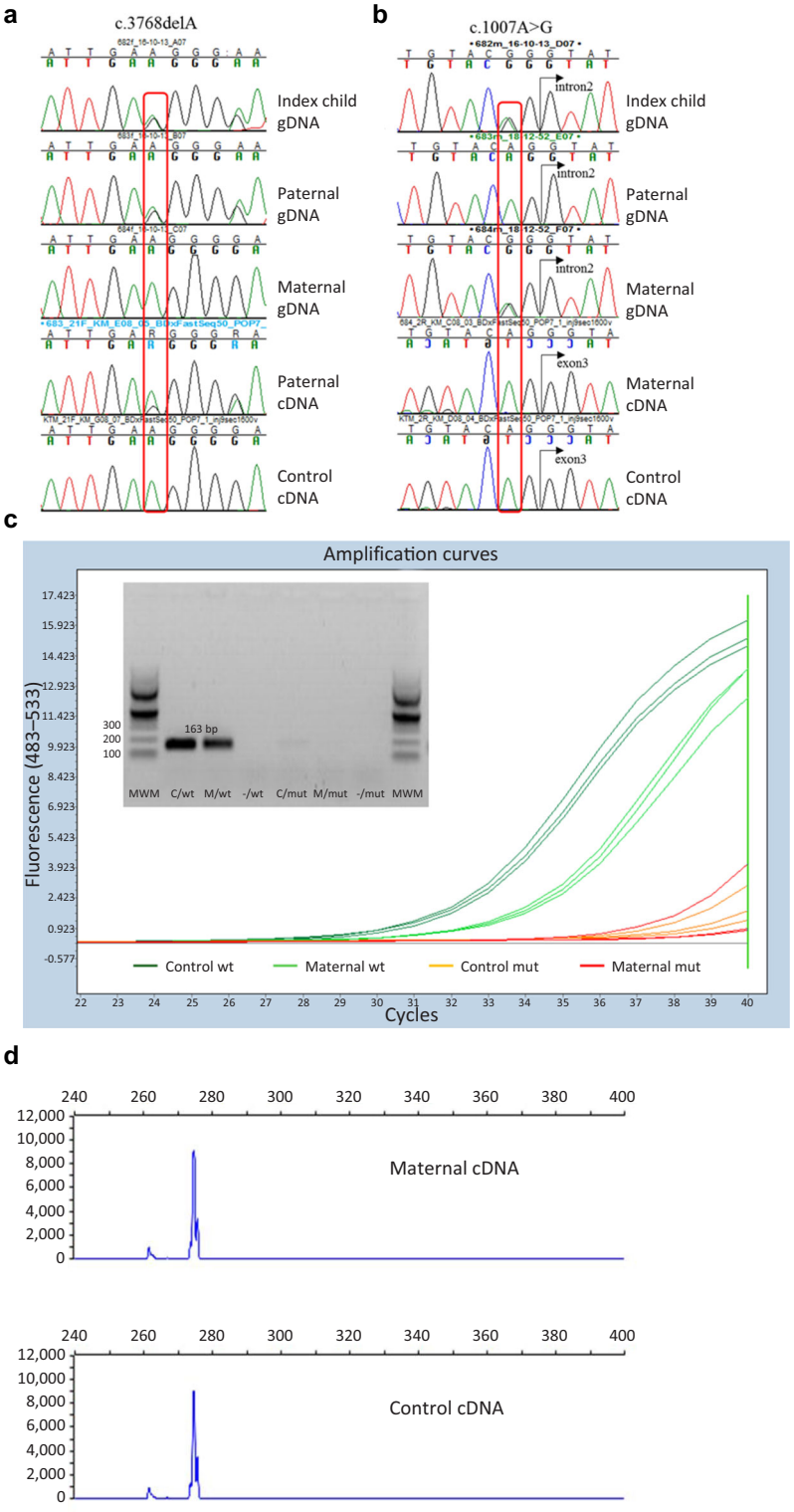

FIGURE 2 Absence of maternal c.1007A > G mRNA and splice isoforms. While a low amount of the paternal c.3768delA messenger RNA (mRNA) is detectable on sequence chromatogram (a), the maternal c.1007A > G mRNA is not (b). (c) Quantitative real-time polymerase chain reaction (PCR) of the mutant and the wild-type (wt) alleles reveal no mutant complementary DNA (cDNA) in the maternal sample. Agarose gel electrophoresis indicate the specific wt bands and confirm the lack of amplification of the mutant cDNA from the maternal sample (C: control cDNA, M: maternal cDNA, mut: mutant allele-specific PCR, MWM: molecular weight marker, wt: wt allele-specific PCR, "-": no template control). (d) Reverse transcription quantitative multiplex PCR of short fluorescent fragment (RT-QMPSF) shows no difference between the control and the maternal samples, indicating the lack of splice isoforms of the c.1007A > G allele [Colour figure can be viewed at wileyonlinelibrary.com]

of amplification (95°C for 15 s, 60°C for 20 s, 72°C for 15 s) and a final extension (72°C for 5 min). Fluorescent amplicons were separated on an ABI prism 3100 genetic analyzer (Thermo Fisher Scientific, Waltham, MA), and the resulting fluorograms were analyzed using the Peak Scanner Software 2.0 (Thermo Fisher Scientific).

3 | RESULTS AND DISCUSSION

The presence of the eight principal features of Vici syndrome (agenesis of the corpus callosum, recurrent infections, cataract, oculocutaneous hypopigmentation, cardiomyopathy, failure to thrive, progressive microcephaly, and

profound developmental delay) was found to have a specificity of 97%, and a sensitivity of 89% for a positive *EPG5* genetic test (Byrne et al., 2016c). In the presented family, the male patient displayed all eight key symptoms in the first 3 months of his life, emphasizing the severe course of the disease. He also developed myopathy, elevated liver enzymes, and intractable seizures, which were previously proposed to be typical features in Vici syndrome. Moreover, he suffered from severe gastroesophageal reflux disease similarly to four previously reported patients for whom Nissen fundoplication or gastrostomy was necessitated (Balasubramaniam et al., 2018; Huenerberg et al., 2016; Shimada et al., 2018; Tasdemir et al., 2016). Gastroesophageal reflux disease may be therefore considered as part of the associated clinical spectrum. Intractable diarrhea developed in the female patient and was suggested to be secondary to malabsorption. This consequence is supposed to be linked to *EPG5*-related autophagy depletion (Alzahrani et al., 2018; Hedberg-Oldfors et al., 2017; Huenerberg et al., 2016; Shimada et al., 2018).

In accordance with the clinical diagnosis, the index patient was found to be compound heterozygous for the maternal c.1007A > G and the paternal c.3768delA *EPG5* mutations (Figure 2a,b). Corresponding to the close localization of the premature stop codon to an exon–intron boundary (38 bp upstream) (Maquat, 2004), we found the paternal mutant mRNA to be only partially decayed (Figure 2). However, the c.3768delA leads to premature truncation, producing a half-length, presumably dysfunctional protein (p.Glu1258Asnfs*3).

The maternal c.1007A > G was not detectable on the sequence chromatogram of the cDNA (Figure 2). Accordingly, we detected no c.1007A > G mRNA by allele-specific qPCR in the maternal sample (Figure 2). Several splice isoforms have been described in a patient with homozygous c.1007A > G, three major ones being present in 72% of the transcripts (Kane et al., 2016). However, we found no alternative splice isoforms by RT-QMPSF in the maternal sample, further supporting the different effect of the c.1007A > G mutation in the presented family (Figure 2).

Based on these findings, the two affected siblings had no functional *EPG5* protein. This contrasts previous findings in the patient with the c.1007A > G mutation in whom 25% of the transcripts are spliced normally, and encode only the p.Gln336Arg substitution (Kane et al., 2016). The two siblings herein presented with early-onset cardiomyopathy, cataract, and severe immunodeficiency: a severe phenotype typical for patients with biallelic loss-of-function *EPG5* mutations, but uncommon in patients with c.1007A > G (Supplemental Table 1). We thus hypothesize that the severe clinical course is explained by the lack of the canonical splicing and a complete mRNA decay. Similarly, a significant interfamilial phenotype variability related to nonconsensus splicing mutations was observed in cystic fibrosis, highlighting that splicing factors can modulate the effect of the mutations on the splicing pattern of *CFTR* alleles (Chiba-Falek et al., 1998; Nissim-Rafinia, Chiba-Falek, Sharon, Boss, & Kerem, 2000). These support that the effect of the nonconsensus splice site mutations may be variable among families.

In conclusion, we infer that there is interfamilial variability in the splicing of the *EPG5* c.1007A > G allele, and the related phenotype can be severe.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

E.V. diagnosed the index patient with Vici syndrome, was involved in his clinical management, and researched current literature. T.M.K. and E.J. performed the qPCR, the RT-QMPSF measurements, and the Sanger sequencing of the cDNA. L.B. supervised the clinical care of the index child. K.T. designed the study. All authors wrote the manuscript and prepared the figures.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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