CASE REPORT

# Vici Syndrome with a Novel Mutation in *EPG5*

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**Background**: Vici syndrome is a neurodevelopmental disorder of the autophagy pathway. Almost all cases reported have the cardinal features of agenesis of corpus callosum, cataract, cardiomyopathy, immunodeficiency and hypopigmentation. **Case characteristics**: 8-month-old boy with developmental delay, myoclonic jerks, repeated respiratory infections, coarse facial features, cataract and hypopigmented hair. Echocardiography revealed dilated cardiomyopathy and magnetic resonance imaging of brain suggested agenesis of corpus callosum. Exome sequencing detected a novel homozygous nonsense mutation in the *EPG5* gene. **Outcome**: Establishing a definite diagnosis helped in proper prognostication, providing genetic counseling and prenatal diagnosis to the family. **Message**: Though uncommon, presence of the characteristic features makes Vici syndrome a clinically recognizable cause of developmental delay.

**Keywords**: *Agenesis of corpus callosum, Autophagy, Cataract, Developmental delay, Hypopigmentation*.

Vici syndrome (OMIM#24280) is a multi-system disorder of the autophagy pathway. The typical phenotype includes severe developmental delay, agenesis of corpus callosum, cardiomyopathy, cataract, generalized hypopigmentation and variable immunodeficiency. Additional features like coarse facies and gingival hyperplasia makes this rare disease a close differential diagnosis of lysosomal storage disorders. Bi-allelic mutation in the *ectopic P-granules autophagy protein 5, (EPG5),* is the underlying etiology. We describe the disease in an infant, with history of similarly affected siblings, and report a novel homozygous mutation in *EPG5* in the proband.

## CASE REPORT

The propositus presented at eight months of age with severe global developmental delay and myoclonic jerks. He had total head lag and no social smile. He also had repeated respiratory tract infections and was hospitalized thrice for pneumonia. He was born at 37 weeks with a birth weight of 2.75 kg and had an uneventful perinatal course. His parents were second cousins once-removed, and he had a deceased elder brother who had similar features.

The proband had a weight of 7 kg (-2 SD), length of 67 cm (-1 to -2 SD) and occipito-frontal circumference of 40 cm (-3 to -4 SD). He had coarse facial features, prominent metopic suture, bitemporal narrowing, frontal upsweep of hair, arched well-defined eyebrows, smooth philtrum, tented upper lip and retrognathia (***Fig.* 1a**). Gingival hyperplasia and cataract in both eyes were also noted. Hair was lighter in color as compared to the parents. He also had tapering fingers, left single palmar crease and brachydactyly, especially of the feet. The liver was palpable 2 cm below right costal margin (span of 5 cm) and firm in consistency. Spleen was not palpable. He did not have any eye contact and responded only to loud noise. There was generalized hypotonia and deep tendon reflexes were not elicitable, but there was no focal neurological deficit.

His blood investigations at various instances showed hemoglobin of 9.6 -10.3 g/dL, platelet count 525-684 x $10^9$/L, total leucocyte count 21.6-25.3 x $10^9$/L with 33-46% neutrophils and 48-58% lymphocytes. The general blood picture was normocytic normochromic with occasional hypochromic microcytic cells. Creatine phosphokinase was raised (358 U/L; normal <190 U/L). Random blood glucose, liver- and renal-function tests were unremarkable. Thyroid profile was normal. There was elevated C-reactive protein (43.6 mg/dL). Tandem mass spectroscopy did not reveal any abnormal metabolite. Serum antibody levels and other immunological work-up could not be performed.

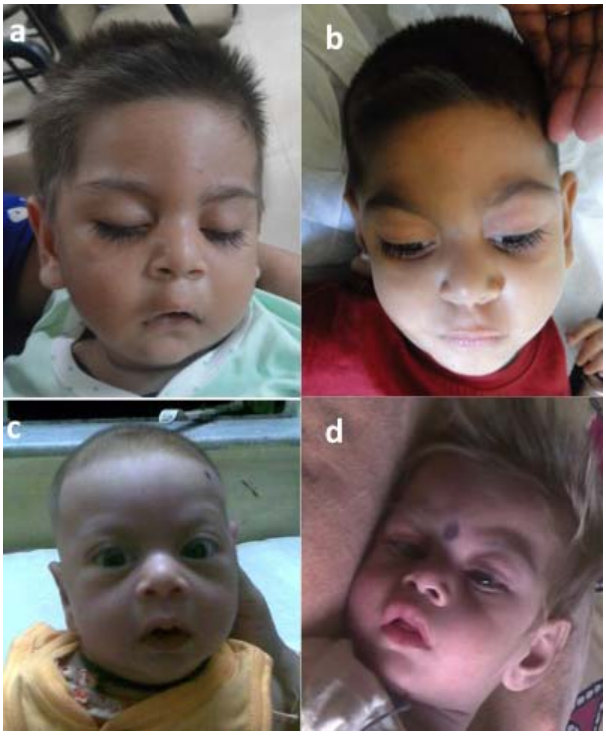


**Fig. 1** *Proband at the ages of 8 months (a); and 3 years (b); proband's elder brother at 3 months (c), and 2 years (d).*

Eye examination showed anterior polar cataract, disc pallor and abnormal visual evoked potentials (VEP) in both eyes. Echocardiography showed features of dilated cardiomyopathy; global left ventricular hypokinesia (ejection fraction 44%) and mild mitral regurgitation. Corpus callosal agenesis with dorsal cyst and mild lag in myelination were noted in magnetic resonance imaging (MRI) of brain (***Web Fig***. **1**). Skeletal radiographs did not show any feature of dysostosis multiplex and urine thin layer chromatography for lysosomal storage disorders was also normal. Enzyme assay for GM1 gangliosidosis, mucopolysaccharidosis type I and mucolipidosis were within normal limits.

Genomic DNA was extracted from the blood of the patient and parents. The libraries were prepared with the NexteraRapid Capture Exome, Illumina and sequenced on HiSeq 4000 platform (Illumina, San Diego, CA, USA). Sequences were aligned to the GRCh37/hg19 human reference genome. The average coverage in the proband was 176x and 97.9 % of the exome was covered at >20x. Bioinformatics analysis identified a homozygous novel variant c.3544G>T (p.Glu1182*) in *EPG5* (NM_020964.2) in the proband. Both parents were heterozygous carriers for the same. Validation of the variant by Sanger sequencing was done in the proband and his parents using ABI 310 capillary sequencer (Applied Biosystems, Foster City, CA, USA).

The proband was again examined at three years of age. He had achieved neck control but could not roll over or sit with support. He did not have any meaningful speech. He had feeding difficulty and had several episodes of respiratory tract infections requiring hospital admission. Hypopigmentation was mild. His facial features had coarsened further (***Fig.* 1b**). Generalized hypotonia persisted but with intermittent episodes of spasticity. He had developed joint contractures of the elbows, wrists, knees, ankles and small joints of the hands.

The elder brother of the proband was also similarly affected and expired at 2 years 3 months. He was not examined personally but his medical records and photographs were reviewed. He was born at 38 completed weeks with a birth weight of 2.7 kg. He had feeding difficulty, hypotonia during the neonatal period. Epicanthal folds, high arched palate and retrognathia were noted. He had severe developmental delay, myoclonic jerks and never achieved head control and social smile. He had recurrent pneumonia and succumbed during such an episode. Photographs showed similar coarseness of facies as the proband (***Fig.* 1 c,d**). He had obvious generalized hypopigmentation. Dysgenesis of corpus callosum and periventricular white matter hypoplasia were noted in MRI brain. VEP was abnormal in both eyes. Biotinidase assay and multiplex PCR for spinal muscular atrophy (SMA) were normal. His tandem mass spectroscopy was unremarkable. His sample was not available for further genetic testing.

Prenatal diagnosis could be provided to the family in the third pregnancy. The mutation was not detected in the fetus and a healthy child was born.

## DISCUSSION

Though several cases of Vici syndrome were reported after it was first described in 1988, the causative gene *EPG5* at 18q12.3 was identified by exome sequencing in 2012 [1]. The largest study of Vici syndrome described 50 patients from 30 families. The cardinal features of developmental delay, agenesis of corpus callosum, cataract, cardiomyopathy, hypopigmentation and skeletal myopathy were present in all cases [2,3]. Inconsistent presence of these features was reported in a recent study from Japan [4].

In the present family, there was some degree of phenotypic variability in the affected siblings. The elder sibling had more profound developmental delay. He also had more severe hypopigmentation which became more obvious with age as opposed to the proband. The arched

and well delineated eyebrows, prominent metopic suture and upsweep of hair giving a characteristic facial phenotype in the proband were not conspicuous in the photographs of the sibling, and also have not been reported previously. In addition, our case had leukocytosis in contrast to the more commonly observed finding of leucopenia [3].

This disorder is one of the emerging group of metabolic disorders known as congenital disorders of autophagy [5]. *EPG5* encodes a protein with an important role in autophagy network which explains the multi-systemic involvement and overlapping features of lysosomal storage disorders. Defective autophagosome-lysosomal fusion has been demonstrated in mice models and more recently in cultured skin fibroblasts of patients [4]. Majority of the mutations reported so far are truncating mutations as also observed in our case. These are distributed throughout the 44 exons and splice sites [1-3,6-8]. Our patient had a nonsense substitution, c.3544G>T (p.Glu1182*) in the 25$^{th}$ exon leading to a premature termination codon. This variant has not been observed in Exac (*exac.broadinstitute.org*), gnomAD (*gnomad.broadinstitute.org*) and 1000 Genomes Project (*internationalgenome.org*). It occurs at an aminoacid that is conserved across species and is predicted to be disease-causing by in-silico analysis (*mutation-taster.org*).

This report adds to the pan-ethnic occurrence of Vici syndrome and highlights intra-familial variability. With more widespread use of next generation sequencing more cases of this under-diagnosed condition could be identified including cases with atypical phenotype and fetal manifestations [9].

*Contributors*: AM: drafting the manuscript, compilation of clinical details of the patient, analysis and interpretation of exome data; KM: procuring patient details and management of the family, and critical inputs to the manuscript; AG: clinical management of the patient; SRP: critical revision and final approval. All authors approved the final version of manuscript and agree to be accountable for authenticity and integrity of the work.

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