

# A Novel *SLCA16A1* mutation in An Infant with Hypoglycemia and Severe Metabolic Ketoacidosis

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## INTRODUCTION

Recurrent episodes of ketoacidosis with or without hypoglycemia have recently been reported with homozygous or heterozygous mutations in the solute carrier family 16 member 1 (*SLC16A1*) gene. This gene encodes for the monocarboxylate transporter 1 (MCT-1) which plays a key role in lactate, pyruvate and ketone body transport. The Objectives of this study is to describe the youngest patient with a novel *SLC16A1* gene who presented with recurrent episodes of acidosis and hypoglycemia.

## CASE REPORT

The patient was born following a NVD, with a birth weight of 3.2kg. At 3 days of age she presented with hypothermia and acidosis. At 6 months of age, she presented again with vomiting and was biochemically noticed to have hypoglycemia and metabolic acidosis. Family history was significant for consanguinity (first degree cousin parents) - Figure 2. The patient has repeated episodes of hypoglycemia and seizures of which an MRI of the head displayed bilateral symmetrical abnormal T2/FLAIR hyperintense white matter signal changes - Figure 3.

## METHODS

Whole Exome Sequencing (WES) analysis was performed in the patient and her parents using NetGen sequencing on an Illumina system. Sequence and copy number alterations were reported according to the Human Genome Variation Society (HGVS) and International System for human Cytogenetic Nomenclature (ISCN) guideline, respectively.

Table 1. Primer Design-*SLC16A1* c.218delG

Forward Primer (Left Primer)	Reverse Primer (Right Primer)
GAGGGAGCAGTTTCCTTTATATT	CTCACCTCCAATGACTCCAA

## RESULTS

Exome sequencing showed that the patient was homozygous for the c.218delG pathogenic variant in the *SLC16A1* Gene (P.Gly73ValfsX8 in exon 3 in the *SLC16A1* gene). The patient's mother and father were heterozygous for the mutation- Figure 1. The c.218delG variant has not been reported previously as a pathogenic variant nor as a benign variant. The c.218delG variant causes a frameshift starting with codon Glycine 73, changes this amino acid to Valine residue and creates a premature Stop codon at position 8 of the new reading frame. This identified variant is anticipated to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. The c.218delG variant is not observed in large population cohorts.



Figure 1: MRI head. Bilateral symmetrical abnormal T2/FLAIR hyperintense white matter signal changes with diffusion restriction is seen mainly involving the superficial subcortical U fibers with an anterior predominance and involvement of the subinsular white matter. The corpus callosum, thalami and basal ganglia are also involved.

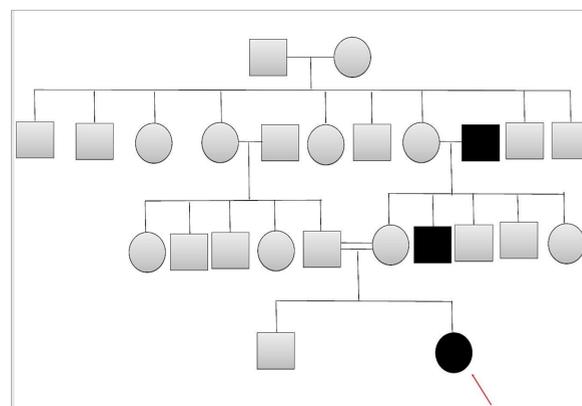


Figure 2: The patient's family pedigree. The chart is significant for consanguinity and a similar phenotype observed in several family members.

## Sanger Sequencing: Two software were used to analyze the results:

- 1 - Applied Biosystems Sequencing Analysis Software v6.0
- 2 - Applied Biosystems SeqScape Software v3.0

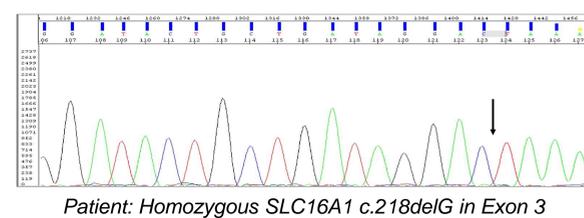
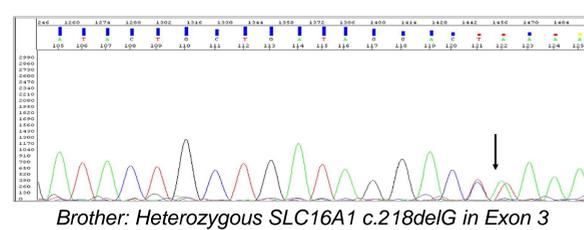
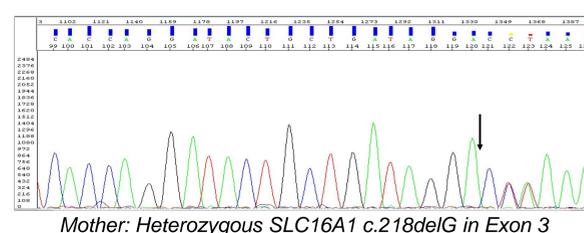
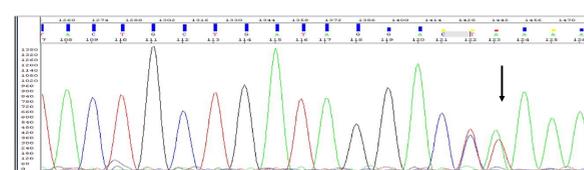


Figure 3: Sanger sequencing of *SLC16A1*. A-C display heterozygosity for c.218delG in Exon 3 of the *SLC16A1* gene. D- the patient is Homozygous *SLC16A1* c.218delG in Exon 3. The Reverse Primer was used in the analysis.

## CONCLUSION

We report a novel mutation in the *SLC16A1* Gene leading to recurrent metabolic acidosis and hypoglycemia. Our patient is one of the youngest presenting with this disorder. Further research will be required to understand the role of the MCT-1 in key tissues such as the liver and muscle and ketone body metabolism. Disruption of MCT1 in the central nervous system produces axon damage and neuronal loss in mice, yet it remains unclear at this stage whether this is a direct effect of the absence of MCT1 in the brain or caused by episodes of profound ketoacidosis. Nevertheless, neurodevelopmental follow up should be considered in this patient.