Mosaic GLUD1 Mutations Associated with Hyperinsulinism Hyperammonemia Syndrome

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\textbf{Keywords}

Hyperinsulinism · Beta cells · Hypoglycemia · Ammonia · Insulin

\textbf{Abstract}

\textbf{Introduction:} The hyperinsulinemia-hyperammonemia syndrome (HIHA) is the second most common cause of congenital hyperinsulinism and is caused by activating heterozygous missense mutations in \textit{GLUD1}. In the majority of HIHA cases, the \textit{GLUD1} mutation is found to be de novo. We have identified 3 patients in whom clinical evaluation was suggestive of HIHA but with negative mutation analysis in peripheral blood DNA for \textit{GLUD1} as well as other known HI genes. 

\textbf{Methods:} We performed next-generation sequencing (NGS) on peripheral blood DNA from two children with clinical features of HIHA in order to look for mosaic mutations in \textit{GLUD1} as well as other known HI genes. NGS was performed on peripheral blood DNA from a woman with a history of HI in infancy whose child had HIHA due to a presumed de novo \textit{GLUD1} mutation.

\textbf{Results:} Mosaic \textit{GLUD1} mutations were identified in these 3 cases at percent mosaicism ranging from 2.7% to 10.4% in peripheral blood. In one case with pancreas tissue available, the mosaic \textit{GLUD1} mutation was present at 17.9% and 28.9% in different sections of the pancreas. Two unique \textit{GLUD1} mutations were identified in these cases, both of which have been previously reported (c.1493c>t/p.Ser445Leu and c.820c>t/p.Arg221Cys).

\textbf{Conclusion:} The results suggest that low-level mosaic mutations in known HI genes may be the underlying molecular mechanism in some children with HI who have negative genetic testing in peripheral blood DNA.

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\textbf{Introduction}

Activating heterozygous missense mutations in \textit{GLUD1} causes hyperinsulinemia-hyperammonemia syndrome (HIHA) and is the second most common cause of congenital hyperinsulinism [1]. \textit{GLUD1} encodes glutamate dehydrogenase (GDH), which is a mitochondrial
enzyme that catalyzes the oxidative deamination of glutamate to alpha-ketoglutarate and ammonia [2]. In the tricarboxylic acid cycle, alpha-ketoglutarate is oxidized further, generating adenosine triphosphate and triggering insulin release. GDH is regulated by several allosteric effectors including leucine, which is an activator [3]. GTP and short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) inhibit GDH [4]. SCHAD is encoded by the HADH gene; biallelic recessive mutations in HADH also cause congenital hyperinsulinism characterized by fasting and protein-induced hypoglycemia but without hyperammonemia [5].

GLUD1 mutations that cause HIHA arise de novo in about 54% of cases, with familial cases showing an autosomal dominant pattern of inheritance [1]. HIHA-causing mutations occur in the allosteric GDH sites and impair the ability of GTP to inhibit GDH activity. This leads to an increase in basal insulin secretion as well as increased leucine-stimulated insulin secretion, resulting in both fasting and protein-induced hypoglycemia which are well-controlled with the K<sub>ATP</sub> channel agonist diazoxide [6]. These patients also have persistent, mild elevation of plasma ammonia in the range of 60–150 μmol/L (102–255 μg/dL).

In addition to expression in pancreatic beta-cells, GDH is highly expressed in the kidney, liver, and brain. Because activation of GDH increases renal, rather than liver, ammonia production, therapies used to treat hyperammonemia in hepatic urea cycle enzyme disorders have little or no effect on HIHA [7]. In fact, the hyperammonemia in HIHA does not appear to cause clinical symptoms and does not require medical intervention. Children with HIHA have an increased risk of atypical absence seizures, behavioral problems, and developmental delay presumably due to increased GDH activity in the brain rather than hypoglycemic episodes [8, 9].

We have previously reported a case with clinical features of HIHA including diazoxide responsive HI and elevated plasma ammonia levels but with negative mutation analysis for GLUD1 in peripheral blood DNA [1]. This case, described in more detail below (patient 2), underwent an elective pancreatectomy, despite being diazoxide responsive, and a GLUD1 mutation was subsequently identified in pancreatic DNA (c.1493c>t/p.Ser445Leu). We have identified mosaic GLUD1 mutations in peripheral blood DNA in two additional cases presented here. These results suggest that mosaic mutations in GLUD1 should be considered in children with phenotypic features of HIHA and negative clinical mutation analysis in peripheral blood DNA.

**Methods**

**Probands**

The diagnosis of HI was based on previously described criteria [10–12]: fasting hypoglycemia accompanied by inadequate suppression of plasma insulin, inappropriate suppression of plasma free fatty acids and β-hydroxybutyrate concentrations, and inappropriate glycemic response to glucagon stimulation. Patients were defined as being responsive to diazoxide if HI could be completely controlled by treatment with diazoxide at doses ≤15 mg/kg/day, as demonstrated by maintaining plasma glucose concentrations ≥70 mg/dL for 12–18 h of fasting and/or by developing appropriate fasting hyperketonemia (beta-hydroxybutyrate ≥2 mmol/L with concurrent plasma glucose <50 mg/dL). In 2 cases who underwent surgical pancreatectomy, diffuse disease was diagnosed based on pancreatic histology of surgical specimens. Diffuse disease is defined by histopathology consistent with abnormal islets containing cells with enlarged nuclei present throughout the pancreas [13].

**Genetic Analysis**

Standard clinical mutation analysis of peripheral blood DNA was performed using a two-tier approach. Tier 1 included Sanger sequencing of the four most common HI genes (ABCC8, KCNJ11, GCK, and GLUD1); follow-up tier 2 testing was performed by NGS for ABCC8, KCNJ11, GCK, GLUD1, UCP2, HNF1A, HNF4A, HADH, and SLC16A1.

Next-generation sequencing (NGS): DNA was isolated from peripheral blood and pancreatic tissue using standard kits following manufacturer’s instructions. Exonic and flanking intronic regions of GLUD1 were PCR amplified and combined in equimolar concentrations prior to NGS (Ion Torrent, Life Technologies, Carlsbad, CA, USA). Resulting variants were visualized in The Integrated Genomic Viewer (IGV, Broad Institute) [14] to ensure there was no strand bias in variant calls, that nucleotides in adjacent regions were called correctly, and that they were not in homopolymer regions (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526203). GLUD1 sequence information is based on GenBank reference sequence NM_005271.3, with nucleotides numbered beginning at the first ATG in exon 1 and amino acid residues numbered beginning from the start of the mature protein. Variants were confirmed by Sanger sequencing as previously described [1].

**Results**

**Clinical Case Summaries and Mutation Analysis**

**Patient 1**

Patient 1 was the product of a 40-week gestation born with an appropriate for gestational age birth weight of 3,710 g. At age 8 months, she developed seizures that were not controlled on anti-epileptic medications. At 14 months of age, she presented to the emergency room following a seizure and was found to have a low plasma glucose concentration of 37 mg/dL. The following month, during an admission to evaluate seizures, she was again...
found to have hypoglycemia. She underwent a diagnostic fast that ended with a plasma glucose of 40 mg/dL and positive glycemic response to glucagon stimulation – consistent with hyperinsulinism. She was discharged on a frequent feeding regimen with glucagon for emergency use. Seizures subsequently resolved around 2 years of age. At 7 years of age, seizures returned, and she was referred to the Children’s Hospital of Philadelphia (CHOP) for evaluation. She underwent a diagnostic fast that ended at 15 h with plasma glucose of 54 mg/dL, suppressed plasma beta-hydroxybutyrate (0.1 mmol/L), and a detectable insulin concentration of 5.7 µU/mL. An oral protein tolerance test (OPTT, 1 g/kg resource protein powder) demonstrated protein-induced hypoglycemia; plasma glucose declined from 74 mg/dL to <20 mg/dL 90 min after ingesting the protein load (normal response: change in glucose <10 mg/dL) [15]. Plasma ammonia concentrations were persistently elevated (44–88.8 μmol/L, normal: 9–33 μmol/L). Acute insulin response testing showed an abnormal response to stimulation with leucine (15 mg/kg), resulting in an increase in plasma insulin of 48 µU/mL from baseline (normal: change in insulin <5 µU/mL) [16, 17]. Based on the phenotypic features, including evidence of fasting and protein-induced hypoglycemia, hyperammonemia, and abnormally high acute insulin response to leucine, she was diagnosed with the HIHA syndrome. Her hypoglycemia was well controlled on diazoxide.

Clinical genetic testing by Sanger sequencing of peripheral blood DNA failed to detect a mutation in GLUD1. Years later, NGS was performed in peripheral blood DNA and identified a previously reported GLUD1 mutation (c.820c>t/p.Arg221Cys [18]) at 8.2% mosaicism (96/1,106 reads) that could subsequently be visualized by Sanger sequencing (Table 1; Fig. 1). She is now 26 years of age and continues to require diazoxide for hypoglycemia but has not had further seizures. Her ammonia levels continue to be frequently elevated, although some ammonia levels have been within the normal range.

**Patient 2**

Patient 2 was born at term with an average for gestational age birth weight of 3,920 g. At age 3 months, she had a tonic-clonic seizure and was found to have a plasma glucose of 23 mg/dL. Subsequent testing led to a diagnosis of hyperinsulinism, and she was treated with diazoxide with good response. At age 11 years, she developed recurrent hypoglycemia following diazoxide discontinuation and was admitted to CHOP for evaluation. After 14 h of fasting, she had a plasma glucose of 47 mg/dL with suppressed plasma beta-hydroxybutyrate (0.03 mmol/L) and free fatty acid concentration (0.21 μM), and inappropriately elevated plasma insulin concentrations (13.1 µU/mL). An OPTT demonstrated protein-induced hypoglycemia; plasma glucose decreased from 115 mg/dL to 50 mg/dL in 45 min following a protein load (normal: change in glucose <10 mg/dL) [15]. The plasma insulin level peaked at 264 µU/mL during the test. Plasma ammonia concentrations were persistently elevated (49.7–70.6 μmol/L, normal: 9–33 μmol/L). Acute insulin response testing demonstrated an exaggerated response to stimulation with leucine (15 mg/kg), resulting in a change in insulin from baseline of 125 µU/mL (normal: change in insulin <5 µU/mL) [16, 17]. Altogether these results were consistent with the HIHA syndrome. However, clinical genetic testing by Sanger sequencing of peripheral blood DNA failed to detect a mutation in GLUD1. Diazoxide was restarted with good control of hypoglycemia. At age 12 years, she underwent an elective 95% pancreatectomy in an effort to discontinue diazoxide due to the family’s concerns related to side effects. Histology showed enlarged and hyperchro-

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**Table 1. Low-level mosaic mutations detected by NGS**

| Patient | Histology | Gene | Mosaic mutation | Functional defect | Minor allele frequency (gnomAD) | Mosaicism by next-generation sequencing (minor/total base calls) |
|---------|-----------|------|----------------|------------------|-------------------------------|---------------------------------------------------------------|
| 1       | No surgery | GLUD1 | c.820c>t/p.Arg221Cys | Activating | 0 | 8.7% (96/1,106) NA |
| 2       | Diffuse   | GLUD1 | c.1493c>t/p.Ser445Leu | Activating | 0 | 10.4% (118/1,130) 17.9%; 28.9% (4,450/24,847; 2,660/9,199) |
| 3b      | Diffuse   | GLUD1 | c.1493c>t/p.Ser445Leu | Activating | 0 | 2.7% (80/2,971) NA |

NA, not available. aPreviously published mutations (PMIDs 11214910, 9571255). bMother of the HI-HA-affected child.
Mosaic GLUD1 Mutations in HIHA

Patient 1
GLUD1: c.820t>c

Patient 2
Blood and pancreas
GLUD1: c.1493t>c

Fig. 1. Sanger confirmation of somatic mutations. Point mutations resulting in amino acid substitutions in GLUD1 were confirmed by bi-directional Sanger sequencing in blood in 2 patients. For each patient, wild-type sequences ±2 bp from the point mutation are shown, as well as sequences of DNA from blood and the whole pancreas where available.

matic nuclei in the beta cells throughout the pancreas, consistent with diffuse-HI. Following her pancreatectomy, she was able to fast for 21 h maintaining her plasma glucose over 70 mg/dL. She fasted for a total of 32.5 h, at which point her plasma glucose was 48 mg/dL, with suppressed plasma beta-hydroxybutyrate (0.66 mmol/L) and free fatty acid concentration (0.76 mmol/L) and inappropriately elevated plasma insulin (5.7 µU/mL). She had an inappropriate glycemic response to glucagon stimulation. These results indicated that she had residual, but improved, hyperinsulinism, and she was discharged without medication. Analysis of pancreatic DNA identified a known disease-causing missense mutation in GLUD1 (c.1493t>c/p.Ser445Leu [6]). NGS in DNA from two regions of the pancreas confirmed the mutation, which was identified at 17.9% (4,450/24,847 NGS reads) and 28.9% (2,660/9,199 NGS reads) mosaicism in the respective regions. Reexamination of the peripheral blood DNA revealed a low level of mosaicism for the same mutation, which was not initially detected (Table 1; Fig. 1). NGS in peripheral blood DNA confirmed the mutation at 10.4% (118/1,130 NGS reads) mosaicism. She is now 32 years of age and continues to experience episodes of hypoglycemia which have been controlled on medication (diazoxide and octreotide at different times) and/or diet.

Patient 3

Patient 3 is the mother of a child who presented with HIHA syndrome at birth. The child was referred to CHOP for management and was found to be heterozygous for a previously reported activating GLUD1 mutation detected in peripheral blood DNA (c.1493t>c/p.Ser445Leu [6]). The mutation was thought to be de novo since it was not detected in DNA from either parent by clinical genetic testing by Sanger sequencing. However, his mother (patient 3) reported a history of hypoglycemia that was treated by pancreatectomy for diffuse-HI when she was a child. She also reported a history of seizures, treated with antiepileptic medication in early childhood, which subsequently resolved. NGS for GLUD1 was performed in peripheral blood DNA from patient 3 (pancreatic DNA was not available), which identified the same GLUD1 mutation that her son has, but at a low level of mosaicism (2.7%, 80/2,971 NGS reads), below the limit of detection for Sanger sequencing (Table 1). Although plasma ammonia levels were not available from patient 3’s initial diagnosis, plasma ammonia levels as an adult were normal, suggesting that her GLUD1 mutation was either not present or present only at very low percent mosaicism, in the kidneys, the presumed source of the hyperammonemia in HIHA syndrome [7].

Discussion

The results of these studies identified mosaic GLUD1 mutations in peripheral blood DNA in 2 patients with clinical features of HIHA, including hypoglycemia and
hyperammonemia, at levels of mosaicism ranging from 8.7 to 10.4%. In one of these 2 patients from whom pancreas tissue was available, the GLUD1 mutation was detected at higher percent mosaicism in two samples of pancreatic DNA (17.9–28.9%). A mosaic GLUD1 mutation was also identified in peripheral blood DNA from a third patient who had a history of hyperinsulinism, and a child with HIHA syndrome, but did not have elevated ammonia levels as an adult. The mutation in this case (patient 3) was present at lower percent mosaicism in peripheral blood (2.7%) compared to the other 2 cases described here. The fact that the combination of clinical features of HI plus hyperammonemia requires involvement of at least two different tissues (pancreatic beta-cells and renal tubular cells) [7, 19] may explain why patient 3, who had HI but normal plasma ammonia levels, also had the lowest level of mosaicism for a GLUD1 mutation in peripheral blood DNA.

Low-level mosaic mutations of known HI genes have been reported in the literature. However, these have all been identified in pancreatic DNA. We previously reported the mosaic GLUD1 mutation identified in patient 2, as well as a mosaic GCK mutation identified in pancreatic DNA in another patient with diffuse HI [1]. The somatic GCK mutation (c.1361_1363dupCGG/p.Ala454dup) was not detected on clinical genetic testing of peripheral blood DNA, done by Sanger Sequencing, and not available for high depth of coverage NGS. It is therefore unknown whether the GCK mutation, in this case, is present in peripheral blood at levels below the limit of detection of the clinical genetic test. In addition, we have also reported low-level mosaic mutations of ABCC8 and GCK identified in pancreatic tissue from six children with histology consistent with localized islet nuclear enlargement [20]. Two other groups have reported mosaic mutations in known HI genes in pancreatic DNA. Houghton et al. reported a case with HI associated with 11pUPD and a somatic mutation in ABCC8 (p.Glu1507Lys) that was detected in lesion tissue by NGS at a level of mosaicism (28% of 419 reads) high enough to be found by Sanger sequencing but was not found in normal regions of the pancreas or in peripheral blood DNA [21]. Henquin et al. [22] reported a patient with histology consistent with localized islet nuclear enlargement-HI and a mosaic GCK (p.Ile211Phe) mutation identified in affected pancreatic tissue; blood and unaffected pancreas were negative for the mutation.

Currently, up to 23 genes have been associated with congenital hyperinsulinism [5, 6, 23–48]. However, approximately 50% of children who are diazoxide responsive do not have mutations in any of the known genes. The results of this study suggest that some of these children may have mosaic mutations in known, rather than novel, genes that are below the limit of detection to be reported. The low-level mosaic mutations in all 3 cases in the present report were not detected by clinical genetic testing and were only detected by NGS utilizing a high depth of coverage.

The possibility of mosaic mutations in one of the dominantly expressed HI genes, such as GLUD1, ABCC8, KCNJ11, and GCK, should be considered in children with genetics negative HI. In some cases, such as those reported by Houghton et al. [21] and Henquin et al. [22], pancreatic DNA may be required to identify the mosaic mutation. However, as we have shown in patients with clinical suspicion of the HIHA syndrome, DNA samples from peripheral blood may be sufficient for detecting mosaic mutations in GLUD1 by more sensitive NGS. As demonstrated by these cases, comprehensive phenotypic characterization, including evaluating the response to protein and other stimuli, through an OPTT or acute insulin response testing, may help to determine the underlying mechanism of disease when a mutation is not detected in peripheral blood.

Identifying mosaic mutations in children with hyperinsulinism has important implications for disease recurrence risk counseling. For the parents of a child with an identified mosaic mutation, there is no predicted recurrence risk for future pregnancies. In contrast, parents of children with mosaic mutations that have not been identified would be counseled that their recurrence risk could be as high as 50%. Our results also raise an important consideration for families with children who have presumed de novo mutations in a dominantly expressed gene. In these families, the possibility should not be excluded that one of the parents harbors the mutation at a low level of mosaicism and may be at risk for hypoglycemia themselves, as was the case in patient 3 presented here.

In summary, mosaic mutations in known HI loci should be considered in patients with HI who have negative mutation analysis in peripheral blood DNA. In two of the three patients presented here, elevated plasma ammonia levels, in combination with hyperinsulinism, suggested an underlying GLUD1 mutation, which was ultimately identified using NGS. In the third patient, who had a history of HI in infancy and a child with HIHA due to a GLUD1 mutation – but did not have elevated plasma ammonia levels – the mosaic mutation was identified in peripheral blood DNA at very low percent mosaicism. In
these cases, highly sensitive NGS was required to identify the mosaic GLUD1 mutation, revealing the need for increased sensitivity in clinical genetic testing in order to detect low-level mosaic mutations.

Statement of Ethics

The study was reviewed and approved by the Children’s Hospital of Philadelphia Institutional Review Board. Written informed consent was obtained from all adult subjects or the parents of child subjects. Assent was obtained when appropriate.

Conflict of Interest Statement

Diva D. De Leon has received research funding from Zealand Pharma, Tiburio Therapeutics, Twist Bioscience, and Crinetics Pharmaceuticals for studies not included in this manuscript. Diva D. De Leon has received consulting fees from Zealand Pharma, Crinetics Pharmaceuticals, Hanmi Pharmaceutical, and Eiger Biopharmaceuticals not related to this manuscript. Charles A. Stanley and Diva D. De Leon are named inventors in patents # USA Patent Number 9,616,108, 2017, USA Patent Number 9,821,031, 2017, Europe Patent Number EP 2120994, 2018, Europe Patent Number EP2818181, 2019. These patents are not related to the work included in this manuscript.

Author Contributions

Kara E. Boodhansingh conducted experiments, acquired and analyzed data, and wrote the manuscript; Elizabeth Rosenfeld acquired data and reviewed the manuscript; Katherine Lord acquired data and wrote the manuscript; N. Scott Adzick acquired data and reviewed the manuscript; Tricia Bhatti acquired and analyzed data and reviewed the manuscript; Arupa Ganguly designed and analyzed experiments and wrote the manuscript; Diva D. De Leon designed and analyzed experiments and reviewed the manuscript; Charles A. Stanley designed research studies, analyzed data, and reviewed the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to patient privacy concerns but are available from the corresponding author (D.D.D.L.) upon reasonable request.

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