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Novel Hypoglycemia Phenotype in Congenital Hyperinsulinism Due to Dominant Mutations of Uncoupling Protein 2 (UCP2)

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HI Associated with Dominant UCP2 mutations

Context: The rarest genetic form of congenital hyperinsulinism (HI) has been associated with dominant inactivating mutations in uncoupling protein 2 (UCP2), a mitochondrial inner membrane carrier that modulates the oxidation of glucose vs amino acids.

Objective: To evaluate the frequency of UCP2 mutations in children with HI and phenotypic features of this form of HI.

Design: We examined 211 children with diazoxide-responsive HI seen at The Children’s Hospital of Philadelphia (CHOP) between 1997 and October 2016.

Setting: CHOP Clinical and Translational Research Center.

Results: We identified five unrelated children with UCP2 mutations out of 211 cases of diazoxide-responsive HI (5/211, 2.4%). These five children were diagnosed with HI before six months of age; diazoxide treatment was only partly effective in three of the five. Among the five cases, four unique mutations were identified: three missense and one splicing mutation. Three mutations were novel and one was previously reported. In-vitro functional assays showed 30-75% decrease in UCP2 activity. Two of the children off diazoxide developed hypoketotic-hypoglycemia after fasting 15-20 hours; a similar trend towards hypoglycemia after fasting 24 hours occurred in four adult carriers. In contrast, both children and two of the four carriers developed symptomatic hypoglycemia four hours following oral glucose. Unusual oscillating glucose and insulin responses to oral glucose were seen in both patients and carriers.

Conclusions: These data indicate that dominant UCP2 mutations are a more important cause of HI than has been recognized and that affected individuals are markedly hypersensitive to glucose-induced hypoglycemia.
PRECIS: We studied 5 children with UCP2 inactivating mutations that cause diazoxide-responsive congenital hyperinsulinism. We found that UCP2 mutation carriers have unusual hyper-sensitivity to glucose-induced hypoglycemia.

Introduction

Congenital hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in infants and children and has been associated with nine genetic loci [1, 2]. The least common genetic type of HI is associated with inactivating mutations in mitochondrial uncoupling protein 2 (UCP2), which has only been reported in two infants [3]. These two unrelated cases, described in 2008 by Gonzalez-Barroso, et al., were discovered to be heterozygous for missense mutations in UCP2 through screening of a group of ten cases of HI with no detectable mutations. Both infants were responsive to treatment with diazoxide and were reported to be able to discontinue therapy at 1-2 years of age. In the ensuing eight years, there have been no reports of any additional cases to confirm the possibility of an association between HI and UCP2.

UCP2 is a mitochondrial inner membrane transporter related to UCP1, a mitochondrial membrane transporter known to leak protons into the mitochondrial matrix and uncouple oxidative phosphorylation for heat production in brown adipose tissue. A recent report by Vozza, et al. from the Palmieri lab showed that UCP2 is not an uncoupling protein, but instead transports protons and phosphate from the cytosol across the inner mitochondrial membrane in exchange for oxaloacetate and malate, intermediates of the TCA cycle, and aspartate (Figure 1) [4]. By reducing the availability of mitochondrial oxaloacetate, UCP2 acts to limit oxidation of glucose in favor of amino acids. This novel role for UCP2 is supported by data in isolated rat pancreatic islets showing that UCP2 overexpression decreases ATP content and inhibits glucose stimulated insulin secretion [5, 6]. Furthermore, RNAi knockdown of UCP2 expression in pancreatic beta-cells increases glucose-stimulated insulin secretion (GSIS) [7].

This new information on the biochemical function of UCP2 in pancreatic beta-cell insulin regulation suggests that UCP2 might be a more important cause of congenital HI than has been recognized, and that there might be specific phenotypic features in patients with hyperinsulinism due to UCP2 mutations. To test these hypotheses, we screened a large panel of children with diazoxide-responsive hyperinsulinism for mutations in UCP2 and characterized the glucose and insulin responses to fasting and oral glucose in a group of patients and carriers found to have inactivating mutations of UCP2. The results suggest that HI due to UCP2 mutations is more frequent and more persistent than currently appreciated and that the dysregulation of insulin secretion may make these patients highly sensitive to glucose-induced hypoglycemia.

Methods

Cases

Since previously reported children with HI due to UCP2 mutations were responsive to treatment with diazoxide, we included probands who were referred to the Children’s Hospital of Philadelphia (CHOP) between 1997 and October 2016 and diagnosed with congenital hyperinsulinism that responded to treatment with diazoxide. No UCP2 mutations have been identified among our cases of diazoxide unresponsive hyperinsulinism. We excluded cases with transient perinatal stress HI. The diagnosis of hyperinsulinism was based on previously described criteria: hypoglycemia associated with inadequate suppression of plasma insulin concentrations and evidence of excessive insulin action including inappropriately suppressed plasma beta-hydroxybutyrate and free fatty acids and an inappropriate glycemic response to glucagon...
stimulation [8]. Patients were considered diazoxide-responsive if fasting hypoglycemia was controlled by diazoxide at doses <15 mg/kg/day as evidenced by maintaining plasma glucose concentrations >70 mg/dL for 18 hours of fasting or appropriate hyperketonemia (beta-hydroxybutyrate > 2 mmol/L) before plasma glucose fell to <50 mg/dL [2].

**Biochemical Studies**

Fasting tests to diagnose or evaluate control of hyperinsulinism by diazoxide were carried out as previously described [9]. Plasma glucose concentrations were measured using a Nova point of care glucose meter and plasma beta-hydroxybutyrate was measured with a Precision Xtra® meter. Fasting tests were terminated for plasma glucose <50 mg/dL or plasma beta-hydroxybutyrate >2.5 mmol/L. At the time of hypoglycemia (plasma glucose <50 mg/dL), blood samples were obtained to measure plasma insulin, beta-hydroxybutyrate, and free fatty acids. Glucagon stimulation tests were performed by administering 1 mg of glucagon intravenous or intramuscular and measuring plasma glucose every 10 minutes for 40 minutes. Tests performed in mutation carrier relatives of probands included a 24 hour fasting test and an oral glucose tolerance test (oGTT) using 75 gm of glucose with measurement of plasma glucose and insulin every 30 minutes for five hours.

**Mutation Analysis**

Genomic DNA was isolated from peripheral blood (5 PRIME, Gaithersburg, Maryland) or from saliva (Oragene DNA self-collection kit; DNA Genotek, Kanata, Ontario, Canada). Coding sequences and intron/exon splice junctions were amplified and directly sequenced on an ABI 3730 capillary DNA analyzer (Applied Biosystems, Carlsbad, California). Sequences were analyzed and compared with the published sequence for UCP2 (NM_003355). Genetic variants were searched against the Genome Aggregation Database (gnomAD) that includes 141,352 unrelated individuals, including 12,942 individuals of African descent, in order to determine population frequency [10]. The functional consequences of novel, missense mutations were predicted with bioinformatics software, SIFT [11], PolyPhen2 [12], and Mutation Taster [13]. Human Splicing Finder was used to predict splicing alterations resulting from intronic mutations [14].

**Functional Analysis of UCP2 Mutations**

To assess the pathogenic potential of the identified UCP2 variants, functional assays were performed using phosphate/aspartate transporter assays as described in Vozza, et al [4]. Wild-type and mutant UCP2 proteins were expressed in E. coli and purified. The same amount of each recombinant protein was used for in vitro reconstitution of the carrier into liposomes. Liposomes were preloaded internally with 20 mM aspartate. Transport was started by addition of 0.5 mM [\(^{33}\)P]-phosphate and terminated after two minutes. The activity of the [\(^{33}\)P]-phosphate/aspartate exchange, i.e. the distinctive transport reaction catalyzed by UCP2, was measured in reconstituted liposomes in 4 independent experiments. Significance was defined as a p<0.05 in difference in activity of mutant vs wild type protein by unpaired t-test.

**Consent**

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 from the parents of subject children.
Results

Mutation Analysis
A total of 211 children with diazoxide responsive HI seen at The Children’s Hospital of Philadelphia between 1997 and October 2016 were screened for mutations in the known HI loci. Mutations in ABCC8, KCNJ11, GCK, GLUD1, HADH, HNF4A, or HNF1A were identified in 100 of these children (47%). Mutations in UCP2 were found in five of the remaining children (5/211, 2.4%).

As shown in Table 1, among these five unrelated patients, four unique UCP2 mutations were identified. Three were coding sequence missense mutations and one was an intronic splicing mutation. Case 1 had a missense mutation (p.Ala268Gly) that had been previously reported by Gonzalez-Barroso, et al [3]; the remaining three mutations were novel. Two of the five unrelated probands shared a novel p.Gly61Ser mutation. In silico prediction software suggested that three of the four mutations would be damaging, while the p.Ser47Asn mutation was predicted to be tolerated [11-13]. The population frequency of all four mutations was low in the total population (0.01 to 0.16%). However, for the three missense mutations, the frequency was slightly increased in the subgroup with African descent, most notably the p.Ala268Gly mutation with a frequency of 1.5% compared to 0.16% in the total population. Conversely, the c.816-2 a>g splicing mutation occurs at a slightly higher frequency in a subgroup with non-Finnish European compared to African descent (0.02% vs 0.00%) [10].

None of the probands’ family members who carried a UCP2 mutation had been diagnosed with hypoglycemia. However, the fathers of cases 1, 4, and 5, as well as the paternal grandmother of case 4, gave histories of frequent episodes of symptoms compatible with hypoglycemia that were relieved by food. Two of these fathers developed symptomatic hypoglycemia during glucose tolerance testing (see below).

In addition to the maternally inherited UCP2 mutation, Case 3 was found to carry a paternally transmitted novel variant of unknown significance in HNF1A which is predicted to be damaging and is not present in online frequency databases. Mutations in HNF1A are associated with MODY3 monogenic diabetes in early adulthood and transient neonatal hyperinsulinism. Despite high risk factors for diabetes (obesity and metabolic syndrome) the father of Case 3 with the HNF1A variant had not developed diabetes at age 38; the younger sister of Case 3, who carried the HNF1A but not the UCP2 variant, had no evidence of neonatal hypoglycemia, despite having been closely monitored. These findings suggest that the HNF1A variant may not be pathogenic, but a possible contribution to HI in Case 3 cannot be ruled out.

The effects of the three missense UCP2 mutations on [33P]-phosphate / aspartate exchange in vitro were assessed in liposomes reconstituted with purified wild-type or mutant UCP2 proteins. As shown in Table 1, liposomes reconstituted with wild-type UCP2 protein catalyzed efficient uptake of [33P]-phosphate similar to that reported previously [4]. In contrast, uptake of [33P]-phosphate was decreased in liposomes reconstituted with the UCP2 proteins harboring the three missense mutations (p-values 0.0001 to 0.03). Similar results were found using phosphate, malate, or oxaloacetate instead of aspartate as the intra-liposomal counter-substrate (data not shown). These observations indicate that the three missense mutations are associated with reduced activity of UCP2, although the degree of reduction in vitro appeared to be only modest (30-75%).

Clinical Characteristics of UCP2-HI
As shown in Table 2, four of the five hyperinsulinism cases with UCP2 mutations were of African descent and one was of Caucasian origin. Birthweight was large for gestational age in
only one of the five cases (Case 1); birthweight was appropriate for gestational age in three (Cases 3, 4, 5) and small for gestational age in one (Case 2). The median age of presentation was seven weeks (range 2 days-6 months). Hypoglycemia was recognized after a hypoglycemic seizure in all but one case (Case 5) who was a premature infant diagnosed at three weeks of age while still in the neonatal intensive care unit. Most of the children were responsive to treatment with diazoxide; however, Case 2 showed only a partial response and required continuous intragastric dextrose for management of hypoglycemia until 11 months of age. This patient had experienced intrauterine growth restriction that can be associated with a perinatal stress form of hyperinsulinism [2] and this may have contributed to the incomplete response to diazoxide.

Based on the suggestion that hypoglycemia in UCP2-HI resolves in early childhood [3], Cases 1 and 3 were taken off diazoxide therapy at 9.5 and 6.5 years of age. However, as described below, both children exhibited evidence of ongoing hyperinsulinemic hypoglycemia during fasting and glucose stimulation tests and both continue to require treatment with diazoxide. Cases 4 and 5 are 2.5 and 1 year of age respectively, and continue to require diazoxide to control hypoglycemia. (More complete descriptions of the five cases are available in the online appendix.)

To evaluate the phenotype associated with UCP2 mutations, responses to oGTT and 24 hour fasting tests were determined in Cases 1 and 3 while off of diazoxide therapy at 6.5 and 9.5 years of age, and in four of the carriers of UCP2 mutations from three families who ranged in age from 14 to 45 years of age. As shown in Table 3 in the online appendix, none of the carriers had diabetes mellitus although all were overweight and had biochemical evidence of insulin resistance. These tests demonstrated evidence of ongoing hyperinsulinism in both children. As shown in Figure 3, Case 1 was able to fast for 20 hours while maintaining plasma glucose levels within the normal range, but failed to show an elevation of plasma beta-hydroxybutyrate before his plasma glucose fell quickly to 56 mg/dL and developing symptomatic hypoglycemia (Fig 3A). During a 24 hour fasting test (Fig 3B), Case 3 also developed symptomatic hypoketotic hypoglycemia and had an abnormal positive glycemic response to glucagon at the time of hypoglycemia, indicating persistence of HI.

As shown in Figure 3, an unusual pattern of oscillating plasma glucose values was observed during the fasting test in Case 3: at 13 hours, the glucose dipped to 59 mg/dL before rising to 89 mg/dL at 17.5 hours and subsequently falling to 39 mg/dL at 22 hours. This oscillating pattern of plasma glucose concentrations was also observed during oGTT in both Cases 1 and 3 (Fig 3 C, D), at the end of which both children became symptomatically hypoglycemic. Plasma insulin levels in Cases 1 and 3 showed an oscillatory pattern during oral glucose tolerance testing that closely matched the oscillations in plasma glucose concentrations. Peak plasma insulin responses to oral glucose challenge in both Cases 1 and 3 were at the upper end of the range normally seen in young children.

Following oral glucose loading, two of the four carriers developed symptomatic hypoglycemia (53 mg/dL in Subject 3-II-2 and 57 mg/dL in Subject 5-II-2). During the 24 hour fast none of the four carriers developed hypoglycemia; however, plasma glucose values were declining toward 70 mg/dL in all four individuals and the father of Case 5 developed symptoms of hypoglycemia at the end of the fast. All four of the carrier relatives exhibited somewhat elevated peak insulin responses to oral glucose, most notable in the sister of Case 3 who had a peak insulin value of nearly 500 µU/mL (Fig 4F, reference normal mean peak insulin 115 µU/mL in lean and 187 µU/mL in obese adolescents [15]). As shown in Figure 4, all of the four carriers of UCP2 mutations showed an oscillatory pattern of plasma glucose concentrations.
similar to that observed in Cases 1 and 3. This was most apparent in the responses to oral glucose shown in Fig 4E, 4F, and 4H, but also seen in the responses to fasting.

DISCUSSION

The results of these studies indicate that inactivating mutations of \textit{UCP2} may be a more common cause of congenital hyperinsulinism than has been previously appreciated. Although no cases have been reported since the original report by Gonzalez-Barroso, et al, in 2008, [3] the five children identified in the Children’s Hospital of Philadelphia series indicates that the frequency of \textit{UCP2} mutations among diazoxide-responsive hyperinsulinism cases (2.4%) is similar to that of other rare forms of hyperinsulinism due to mutations in \textit{HNF4A} (2%), \textit{HNF1A} (3%), or \textit{HADH} (2%) [16]. In contrast to the original report, the experience with our series of five cases shows that the hyperinsulinism in patients with \textit{UCP2} mutations does not quickly nor completely resolve, but can persist through childhood or longer. A distinctive feature found in our cases and their carrier relatives was that, in addition to fasting hypoglycemia, oral glucose loading could also provoke profound hypoglycemia.

The function of UCP2 has recently been clarified in studies by Vozza, et al., to differ from that of UCP1, which uncouples oxidative phosphorylation by leaking hydrogen ions across the inner mitochondrial membrane [4]. Instead, as shown in Figure 1, UCP2 acts to transport oxaloacetate, malate, and aspartate out of the mitochondrial matrix and moves phosphate and hydrogen ions from the cytosol into mitochondria. By depleting the pool of mitochondrial TCA cycle intermediates, increases in UCP2 activity tend to restrict glucose oxidation in favor of the oxidation of glutamine and amino acids. Complete ablation of UCP2 activity in \textit{UCP2} knockout mice leads to hypoglycemia resulting from increased glucose stimulated insulin secretion in response to higher ATP production [17]. Thus, the mutations in \textit{UCP2} found in our five patients with hyperinsulinism may enhance the oxidation of glucose in pancreatic beta-cells leading to amplification of the insulin response to glucose. This mechanism is consistent with the observation of large insulin responses to oral glucose, which we observed in two patients and in three out of the four carriers who were tested. Heightened sensitivity of the beta-cell to glucose loading may explain the rather severe postprandial hypoglycemia observed in Cases 1 and 3 three to four hours after oral glucose challenge.

The oscillations in the plasma concentrations of insulin and glucose during the oGTT in Cases 1 and 3 and most of the adult \textit{UCP2} carriers, as well as the similar oscillatory pattern of insulin and glucose during fasting in Case 3 are worth noting (Fig 3 and 4). Biphasic or triphasic patterns of glucose response to oral glucose occur in a minority of normal individuals and appear to be associated with better insulin sensitivity and beta-cell function and lower risk of developing type 2 diabetes mellitus in obese adults and adolescents [18-20]. The relationship of oscillatory insulin and glucose responses and post-glucose symptomatic hypoglycemia in patients with \textit{UCP2} mutations remains speculative. Although mild reactive hypoglycemia after oral glucose is not uncommon in adults, the severe symptomatic post-prandial hypoglycemia seen in our cases with \textit{UCP2} mutations is extremely rare in children that have not had gastric surgery and appears to be a distinguishing feature of hyperinsulinism due to \textit{UCP2} mutations.

In contrast to several of the other forms of congenital hyperinsulinism, fetal overgrowth (large for gestational age birthweight) was not a common finding in our five patients with \textit{UCP2} mutations. This is consistent with the defect primarily producing an exaggeration of the insulin response to a glucose load, rather than persistent hyperinsulinemia in the basal state. Heightened responsiveness to glucose-stimulated insulin release may explain why three out of the five
children with UCP2 hyperinsulinism in our series had difficulty achieving adequate glycemic control even on high doses of diazoxide. In retrospect, it is possible that their apparent poor response to diazoxide may have been due to episodes of postprandial, rather than fasting hypoglycemia. Note that, while not on diazoxide (Fig 3), both Cases 1 and 3 became hypoglycemic only after prolonged fasting but had quite dramatic hypoglycemia following oral glucose. This suggests that evaluation of the efficacy of diazoxide therapy in patients with UCP2 deficiency requires assessing responses to carbohydrate loading as well as the usual testing of fasting tolerance.

An unexplained feature of our UCP2 cases is that four of the five were of African descent. While the number of cases is small, this is striking since individuals of African descent account for only 15% of all diazoxide responsive cases seen at CHOP. It is interesting that the UCP2 mutations in these four patients, particularly the p.Ala268Gly variant, are reported to occur at increased frequency in African populations; whether this reflects a founder effect or some potential advantage in carriers of the variants is unknown.

Several pieces of evidence supporting the interpretation that the UCP2 mutations found in our cases are disease-causing include: 1) identification of identical mutations in two pairs of affected children (p.Ala268Gly and p.Gly61Ser), 2) histories of hypoglycemic symptoms in three adult mutation carriers and documented hypoglycemia during fasting in one of these, 3) similarities in responses to oral glucose and fasting among affected and “unaffected” mutation carriers, 4) evidence that the mutations are associated with decreased UCP2 function, albeit modest, from expression studies in vitro, and 5) new information clarifying the potential pathophysiologic role of UCP2 impairment. Limitations of evidence that the UCP2 mutations found in our patients are disease-causing include the surprisingly modest reductions in UCP2 activity found in expression studies of the three missense mutations and the fact that two of the mutations, especially p.Ala268Gly, occur in as high as 1.5% of asymptomatic individuals of African descent. While the 30-75% reduction found in UCP2 transport activity seems unusually modest for a disease-causing dominant defect, the degree of functional compromise necessary to cause insulin dysregulation in human islets in vivo is not known; it is also possible that the mutations in UCP2 alter insulin regulation via mechanisms not reflected by the in vitro assay of activity. While it seems unlikely for a disease-causing defect to affect 1.5% of the population, HI associated with UCP2 mutations, similar to other dominant forms of HI such as mutations of GLUD1 and ABCC8 [21, 22], may cause mild enough disease to escape recognition and have no noticeable impact on reproductive capacities.

Conclusions:
The results of these studies confirm that inactivating mutations of UCP2 are associated with a dominant, diazoxide-responsive form of congenital hyperinsulinism. UCP2 hyperinsulinism is at least as common as other better-known rare causes of the disorder and should be considered in genetic mutation screening for children with hyperinsulinism. Children with UCP2 hyperinsulinism may require diazoxide treatment for long periods, perhaps indefinitely. The results of these studies suggest that UCP2 plays an important role in coordinating glucose stimulated insulin secretion that may be relevant to diabetes and postprandial hypoglycemia. Children with hyperinsulinism due to UCP2 mutations appear to be highly susceptible to developing hypoglycemia after a glucose load. Therefore, evaluation of treatment should include monitoring the response to oral carbohydrate.
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References


Figure 1. UCP2 modulates beta-cell insulin secretion. UCP2 activity increases oxaloacetate to enhance glucose oxidation and restrain the oxidation of amino acids via glutamate metabolism to alpha-ketoglutarate. GCK: glucokinase; KIR6.2, SUR1: ATP-dependent potassium channel.

Figure 2. Pedigrees of five children with hyperinsulism associated with mutations in UCP2. Arrows indicate probands diagnosed with hyperinsulism. DNA was unavailable for testing in individuals without a number. Black filled symbols: hypoglycemia diagnosed. Diamond symbol: multiple individuals not tested. *Case 3 also carried a paternally inherited novel variant of unknown significance in HNF1A (p.Gly574Asp) (see text).

Figure 3. 24 hour fasting and oral glucose tolerance tests in two children with UCP2 hyperinsulism. Cases 1 and 3 underwent testing at ages 6.5 and 9.5 years old, respectively, after discontinuation of diazoxide treatment. Symbols show plasma glucose (solid line, circle), insulin (dotted line, triangle), and beta-hydroxybutyrate (dashed line, diamond). BOB = beta-hydroxybutyrate; oGTT = oral glucose tolerance test.

Figure 4. 24 hour fasting and oral glucose tolerance tests in in four UCP2 mutation carriers. Carrier family members of Cases 3, 4 and 5 (ages 36, 14, 37, and 45 years; 3-II-2, 3-III-1, 4-II-2, 5-II-2 in Figure 2) underwent testing (details shown in Table 3 in online appendix). Symbols show plasma glucose (solid line, circle), insulin (dotted line, triangle), and beta-hydroxybutyrate (dashed line, diamond). BOB = beta-hydroxybutyrate; oGTT = oral glucose tolerance test.

Table 1. UCP2 mutations found in 5 children with diazoxide-responsive hyperinsulism.

<table>
<thead>
<tr>
<th>Case</th>
<th>Nucleotide</th>
<th>Amino Acid</th>
<th>Population Frequency</th>
<th>In Silico Prediction</th>
<th>Pi/Asp Exchange Rate (mmoles/min/g prot) (n=4, m ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td></td>
<td>(n=4, m ± SD)</td>
</tr>
<tr>
<td>1</td>
<td>c.803 C&gt;G</td>
<td>p.Ala268Gly</td>
<td>0.16%</td>
<td>Damaging</td>
<td>0.85+/-0.11 (p=0.0001)</td>
</tr>
<tr>
<td>2, 5</td>
<td>c.181 G&gt;A</td>
<td>p.Gly61Ser</td>
<td>0.01% 0.10%</td>
<td>Damaging</td>
<td>1.57+/-0.25 (p=0.0012)</td>
</tr>
<tr>
<td>3</td>
<td>c.140 G&gt;A</td>
<td>p.Ser47Asn</td>
<td>0.03% 0.31%</td>
<td>Tolerated</td>
<td>2.27+/-0.41 (p=0.0295)</td>
</tr>
<tr>
<td>4</td>
<td>c.816-2 A&gt;G</td>
<td>-</td>
<td>0.02% 0.00%</td>
<td>Damaging</td>
<td>-</td>
</tr>
</tbody>
</table>

*Previously reported in a child with hyperinsulism [3].

Table 2. Clinical phenotype of five children with UCP2 mutations.

<table>
<thead>
<tr>
<th>Case</th>
<th>Ethnicity</th>
<th>Birth Weight</th>
<th>Age at Presentation</th>
<th>Diazoxide Responsiveness</th>
<th>Age Trialed off Diazoxide</th>
<th>Current Age (yr)</th>
<th>Current HI Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>African American</td>
<td>4.7 kg (&gt;97%ile)</td>
<td>6 months</td>
<td>Yes</td>
<td>9.5 years</td>
<td>11</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>2</td>
<td>African American</td>
<td>2.6 kg (&lt;3%ile)</td>
<td>2 days</td>
<td>Partial</td>
<td>11 months</td>
<td>6.5</td>
<td>unknown</td>
</tr>
<tr>
<td>3</td>
<td>African American</td>
<td>3.7 kg (65%ile)</td>
<td>7 weeks</td>
<td>Yes</td>
<td>6.5 years</td>
<td>8</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>4</td>
<td>Western European</td>
<td>4.0 kg (70%ile)</td>
<td>4 months</td>
<td>Yes</td>
<td>-</td>
<td>2.5</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>5</td>
<td>African American</td>
<td>1.2 kg (31%ile)</td>
<td>3 months</td>
<td>Yes</td>
<td>-</td>
<td>1</td>
<td>Diazoxide</td>
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</table>