Paracentric Inversion of Chromosome 21 Leading to Disruption of the *HLCS* Gene in a Family with Holocarboxylase Synthetase Deficiency

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Abstract Holocarboxylase synthetase (HLCS) deficiency is a rare autosomal recessive disorder that presents with multiple life-threatening metabolic derangements including metabolic acidosis, ketosis, and hyperammonemia. A majority of HLCS deficiency patients respond to biotin therapy; however, some patients show only a partial or no response to biotin therapy. Here, we report a neonatal presentation of HLCS deficiency with partial response to biotin therapy. Sequencing of *HLCS* showed a novel heterozygous mutation in exon 5, c.996G>C (p. Gln332His), which likely abolishes the normal intron 6 splice donor site. Cytogenetic analysis revealed that the defect of the other allele is a paracentric inversion on chromosome 21 that disrupts *HLCS*. This case illustrates

that in addition to facilitating necessary family testing, a molecular diagnosis can optimize management by providing a better explanation of the enzyme's underlying defect. It also emphasizes the potential benefit of a karyotype in cases in which molecular genetic testing fails to provide an explanation.

Introduction

Biotin is a water-soluble vitamin that acts as the coenzyme of four carboxylases involved in gluconeogenesis, fatty acid synthesis, and the catabolism of several amino acids: acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase. Biotin activates the four inactive apocarboxylases through a covalent bond that is catalyzed by holocarboxylase synthetase (HLCS) in a two-step process. In the first step, HLCS activates the carboxyl group of biotin with the addition of an adenylate group to form the reaction intermediate biotinyl-5'-AMP. In the second step, the biotin moiety of biotinyl-5'-AMP is transferred to one of the apocarboxylases (Chapman-Smith and Cronan 1999).

HLCS deficiency (OMIM #253270) is an autosomal recessive disorder that presents with multiple life-threatening metabolic derangements including metabolic acidosis, ketosis, and hyperammonemia. Characteristic findings are similar to those in other organic acidurias and include tachypnea, hypotonia, lethargy, vomiting, and seizures (Sweetman et al. 1982). In addition, cutaneous symptoms that range from periorificial and erythrodermic dermatitis to alopecia are frequently observed (Esparza et al. 2011).

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The majority of HLCS patients respond to biotin therapy. However, a few patients show only a partial or very limited response to biotin therapy depending on the genotype (Peters et al. 2000; Santer et al. 2003; Wilson et al. 2005; Van Hove et al. 2008). Thus, obtaining a molecular diagnosis can result in optimized management by providing a better understanding of the underlying enzyme defect and the extent to which a response to biotin therapy is anticipated.

Here, we describe a patient with a neonatal presentation of HLCS deficiency with partial response to biotin therapy and two novel *HLCS* aberrations. Sequencing of *HLCS* revealed a novel heterozygous variant in exon 5, c.996G>C (p.Gln332His), which may abolish the normal intron 6 splice donor site. Cytogenetic analysis revealed a paracentric inversion on chromosome 21 that was shown by FISH analysis to disrupt the other *HLCS* allele. Familial testing for these variants unexpectedly showed an additional pathogenic variant in the patient's mother, which was also passed onto the patient's sibling. Further familial analysis allowed for a number of interesting conclusions regarding the genotype–phenotype correlation of the family's *HLCS* aberrations.

Case Report

The infant boy was born by vaginal delivery at term to a 29-year-old gravida 5 para 2 mother after an uncomplicated pregnancy. Apgar scores and cord blood gases were normal. Birth parameters included a weight of 2.63 kg (<3rd centile), a length of 49.5 cm (43rd centile), and a head circumference of 33 cm (9th centile). The family history (Fig. 1) includes a mother of Korean ancestry who was adopted without further details known. She is healthy except for a history of palmar hyperkeratosis. The paternal ancestry is Italian, Irish, and French Canadian with no consanguinity present between the patient's parents. There is a known chromosome 21 inversion present in the paternal grandmother that was identified as part of workup for advanced maternal age. The patient also has a healthy 1-year-old sister whose newborn screen was normal. She has a history of hypopigmented hyperkeratotic skin lesions of uncertain etiology.

The patient was initially alert and fed well but within hours of delivery he developed poor feeding, tachypnea, and grunting. Physical exam was otherwise normal. An echocardiogram was only notable for a small patent foramen ovale and a patent ductus arteriosus. A cranial ultrasound showed multiple cystic lesions at the frontal horn and caudal thalamic notches of variable sizes that suggested multiple choroid plexus cysts or an intrauterine

hematoma with resolving cystic change. The serum glucose level and oxygen saturation were normal. A capillary blood gas analysis revealed metabolic acidosis with a pH of 7.12 and an anion gap of 32 meq/L. Plasma lactate was 13.2 mmol/L (normal 0.5–2.2 mmol/L) with an elevated lactate:pyruvate ratio of 65 (normal < 25). Initial ammonia level was 136 μ mol/L and quickly decreased with resuscitation. Plasma amino acids were within normal limits. Semiquantitative urine organic acids (compound peaks compared to an internal standard) showed massive amounts of lactic acid, very large amounts of 3-hydroxyisovaleric acid, large amounts of 3-methylcrotonylglycine, and a small amount of methylcitric acid. Newborn screening performed in the state of Michigan and drawn at 25 h of life showed a 3-hydroxyisovalerylcarnitine/2-methyl-3-hydroxybutyrylcarnitine (C5-OH) level of 3.45 μ mol/L (<1.0 μ mol/L) and a propionylcarnitine (C3) level of 7.1 μ mol/L (<4.0 μ mol/L), consistent with multiple carboxylase deficiency. A serum biotinidase enzyme assay was normal, suggesting a diagnosis of HLCS deficiency.

Empiric treatment with biotin 5 mg daily was started on the first day of life due to lactic acidosis and increased to 10 mg daily divided into two doses on day 3 when biochemical data supported the diagnosis of HLCS deficiency. Dietary protein was restricted to 1.5 g/kg/day. Tachypnea resolved and lactate slowly decreased to 5.5 mmol/L upon discharge on day 9.

At 2 years of age, he has had two hospitalizations for lactic acidosis, though not accompanied by clinical decompensation. During these hospitalizations, the biotin dose was increased to control lactic acidosis with noted decreases in lactate concentrations. Developmentally, he displays only mild expressive language delay. Current growth parameters include a weight of 12.7 kg (76th centile), a length of 81.4 cm (6th centile), and a head circumference of 51.7 cm (>95th centile). His physical exam is otherwise normal. He is maintained on carnitine 100 mg/kg/day and sodium bicarbonate titrated between 1 and 3 meq/kg/day. Biotin has been continued at a dose of 30 mg twice daily, which has maintained lactic acid levels in a range from 2.6 to 12.1 mmol/L during well periods and episodes of biochemical decompensation, respectively. The patient's biochemical labs were repeated during hospitalizations and during times of clinical stability and continued to show the presence of multiple abnormal metabolites at approximately the same relative concentrations (data not included).

Confirmation of the biochemical diagnosis by lymphocyte carboxylase enzyme activity assay, obtained during a period of biochemical stability, demonstrated significantly decreased activity of propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, and pyruvate carboxylase

Fig. 1 Pedigree of the proband

(Table 1). Sequencing of the *HLCS* gene showed a heterozygous missense variant, c.996G>C (p.Gln332His). This residue is highly conserved and the last amino acid encoded in exon 5. The variant alters the terminal guanine and likely abolishes the normal intron 6 splice donor site. Three bioinformatics tools, SIFT, PolyPhen-2, and MutationTaster, predict the p.Gln332His change to be “not tolerated,” “probably damaging,” and “disease causing,” respectively. A deletion and amplification analysis of *HLCS* via array comparative genomic hybridization was normal.

A karyotype was also obtained and revealed the same chromosome 21 paracentric inversion previously identified in the paternal grandmother (Fig. 2a). Subsequent fluorescent in situ hybridization (FISH) studies showed that the breakpoint was between the RP11-166F15 and the 24H16 loci, which are directly flanking and somewhat overlapping the *HLCS* gene proximally and distally (Fig. 2c). The FISH signal with probe RP11-383L18, which hybridizes entirely within the *HLCS* locus, was split (Fig. 2d), indicating that *HLCS* is disrupted by the inversion. The *HLCS* missense variant and the paternally inherited chromosome 21 inversion were therefore determined to be the molecular cause of the patient’s *HLCS* deficiency.

Targeted molecular testing confirmed that the patient’s mother carried the c.996G>C (p.Gln332His) variant. In addition, she was identified to have two additional variants: c.834T>C, a homozygous known synonymous benign variant, and c.565T>C (p.Cys189Arg), a heterozygous

variant of unknown significance in *trans* with the c.996G>C (p.Gln332His) variant as it was not identified in her son. The p.Cys189 residue is fairly conserved across *HLCS* proteins; while a cysteine can be found at this position in many mammalian species, a leucine can be found at this position in nematode and fruit fly, and a valine can be found at this position in yeast. The amino acid change is nonconservative with the cysteine residue changed to a positively charged arginine. The variant is extremely rare, as it is not present in the Exome Aggregation Consortium (ExAC) database, dbSNP, or Exome Variant Server (EVS). The bioinformatics tools SIFT, PolyPhen-2, and Mutation Taster all predict the p. Cys189Arg substitution to be “deleterious.” The mother is entirely asymptomatic except for palmar punctate keratitis, with no history to suggest a previous metabolic decompensation. Biochemical labs including lactate, plasma amino acids, semi-quantitative urine organic acids, plasma acylcarnitine profile, and serum biotinidase activity were all normal except for a mild elevation of propionylcarnitine at 0.97 $\mu\text{mol/L}$ (normal < 0.88 $\mu\text{mol/L}$) and urine organic acids that showed a small amount of 3-hydroxyisovaleric acid and a trace amount of 3-methylcrotonylglycine. These results interpreted together were consistent with multiple carboxylase deficiency. A lymphocyte carboxylase enzyme activity assay confirmed mild *HLCS* deficiency with propionyl-CoA carboxylase activity of 9.1 pmol/min/mg protein (normal ≥ 70), 3-methylcrotonyl-CoA carboxylase

Table 1 Patient characteristics

Patient	Disease severity	Lactic acid (mmol/L; $N < 2.2$)	Ammonia ($\mu\text{mol/L}$; $N < 60$)	UOA abnormalities	ACP abnormalities ($\mu\text{mol/L}$)	PCC activity ($N > 70$)	3-MCC activity ($N > 31$)	PC activity ($N > 6$)	Genotype
Proband	Severe	13.2	136	Lactate 3-Hydroxybutyrate Acetoacetate 3-Hydroxyisovalerate 3-Methylcrotonylglycine Methylcitrate	C3: 160.39 ($N < 0.870$) C5-OH: 2.346 ($N < 0.110$)	8.67	2.84	0	p.Gln332His 46,XY,inv(21) (q21.1q22.13)
Proband's mother	Mild	1.7	—	3-Hydroxyisovalerate 3-Methylcrotonylglycine	C3: 0.970 ($N < 0.880$)	9.1	2.1	5.5	p.Cys189Arg p.Gln332His
Proband's sister	Mild	1.3	—	None	None	40	2	7	p.Cys189Arg 46,XY,inv(21) (q21.1q22.13)

UOA Urine organic acid, ACP Acylcamitine profile, PCC Propionyl-CoA Carboxylase (pmol/min/mg protein), 3-MCC 3-Methylcrotonyl-CoA Carboxylase (pmol/min/mg protein), PC Pyruvate Carboxylase (pmol/min/mg protein)

activity of 2.1 pmol/min/mg protein (normal ≥ 31), and pyruvate carboxylase activity of 5.5 pmol/min/mg protein (normal ≥ 6) (Table 1). Full *HLCS* gene sequencing was performed and no additional variants were identified. Based on the combination of biochemical abnormalities, dermatologic findings, and the analysis of the mother's *HLCS* variants, which were felt to be pathogenic, the patient's mother was diagnosed with mild *HLCS* deficiency, started on 5 mg of biotin, provided with an emergency room protocol and will be followed regularly in the biochemical genetics clinic.

The patient's sister was also evaluated and found to carry the chromosome 21 inversion. *HLCS* molecular testing showed that she also carries the c.565T>C (p.Cys189Arg) variant identified in her mother but as expected not the c.996 G>C (p.Gln332His) variant. Lymphocyte carboxylase enzyme activity was performed and was consistent with mild multiple carboxylase deficiency with propionyl-CoA carboxylase activity of 40 pmol/min/mg protein (normal ≥ 70), a 3-methylcrotonyl-CoA carboxylase activity of 2 pmol/min/mg protein (normal ≥ 31), and a pyruvate carboxylase activity of 7 pmol/min/mg protein (normal ≥ 9) (Table 1). Biochemical labs including lactate, urine organic acids, and plasma amino acids were all within normal limits. Given the molecular results and enzymatic testing she was placed on biotin 5 mg daily and provided with an emergency room protocol.

Methods

Patient

Exempt-status was granted by The University of Michigan's Institutional Review Board. Informed consent was obtained from all patients for which potentially identifying information is included in this article.

Molecular

Sequencing and deletion and amplification analysis of *HLCS* was performed by Prevention Genetics (Marshfield, WI).

Cytogenetic

Chromosome analysis was performed at the 550-band level of resolution using the GTG banding method. FISH was performed using BAC probes RP11-166F15 (chr21:38,044,629-38,215,919; hg19) (BlueGnome, UK), RP11-24H16 (chr21:38,291,517-38,442,545; hg19) (BlueGnome, UK), RP11-383L18 (chr21:38,187,159-

FISH analysis showing the breakpoint of the inversion is proximal to the RP11-24H16 locus (*red*) and distal to the RP11-166F15 locus (*green*) as it hybridized more proximal to its normal location (*white arrow*). **(d)** FISH analysis showing that the breakpoint occurred within the RP11-383L18 locus (*green*) as it hybridized to both its normal location and a more proximal location (*red arrow*).

intervals, based on frequency distribution of control results obtained over each interval.

Discussion

Our patient demonstrated the classic biochemical and clinical findings associated with HLCS deficiency and harbored two novel aberrations of the *HLCS* gene. His clinical presentation included tachypnea and poor feeding but no significant skin involvement. Cranial ultrasound also demonstrated subependymal cysts, a finding observed in most reported cases of holocarboxylase deficiency due to the p.L216R pathogenic variant (Wilson et al. 2005; Slavin et al. 2014). His partial response to high dose biotin (60 mg daily) is evident by the age-appropriate developmental skills and normal physical examination but with persistently elevated lactic acid concentration and abnormal metabolites on urine organic acids.

Currently, there are 41 pathogenic variants reported in *HLCS* (<http://www.hgmd.cf.ac.uk>, accessed June 2016; Aoki et al. 1999; Yang et al. 2001). Biotin responsive

patients often have pathogenic variants identified within the biotin-binding domain (between amino acids 448 and 701), causing an increased K_m for biotin (Suzuki et al. 1994). Biotin supplementation in these patients overcomes this increased K_m restoring enzymatic activity. These patients are clinically asymptomatic on the suggested dose of biotin 10–20 mg daily and require no additional therapies, such as protein restriction or carnitine supplementation with good clinical outcomes documented with biotin doses as low as 1.2 mg daily (Dupuis et al. 1999; Bailey et al. 2008; Tammachote et al. 2010). Conversely, individuals with pathogenic variants outside of the biotin-binding domain are considered biotin-unresponsive and are the most severe cases (Mayende et al. 2012). These patients display normal biotin affinity but a decreased HLCS V_{max} (Suzuki et al. 1994). Though these variants are labeled as biotin-unresponsive, all patients to date with HLCS deficiency display some degree of clinical responsiveness, though this response may only be partial as evident by persistent excretion of abnormal metabolites (Suzuki et al. 1994). This clinical improvement may be due to biotin's ability to increase transcription of the *HLCS* gene and/or the observation that the maximum activity of HLCS occurs at supraphysiologic biotin concentrations (Aoki et al. 1997; Solórzano-Vargas et al. 2002). In line with this observation, very large doses of biotin (i.e. 1.2 g daily) have been found to ameliorate symptoms in individuals homozygous for the p.L216R variant, a non- K_m -variant which causes one of the most severe forms of HLCS deficiency (Slavin et al. 2014).

The patient described here was found to have two novel pathogenic variants in the *HLCS* gene making it difficult to predict how these alterations respond to biotin therapy. The paracentric inversion disrupts transcription of the *HLCS* allele and is predicted to result in a complete absence of functional HLCS protein. Importantly, the presence of two null-variants has been suggested to result in perinatal lethality, as no patients harboring two null variants have been identified to date (Suzuki et al. 1994). This suggests that the p.Gln332His variant, though predicted to disrupt splicing, likely results in the production of at least some functional protein (Suzuki et al. 1994). This residual protein, though harboring a non- K_m -variant, has shown partial responsiveness to biotin supplementation clinically.

In our case, the molecular diagnosis allowed for familial testing which surprisingly identified the patient's mother and sister to also be affected with mild HLCS deficiency. Interestingly, the patient's mother was found to have a novel, nonconservative missense variant, p.Cys189Arg, in addition to the likely pathogenic variant, p.Gln332His. Enzymatic analysis confirmed the mild HLCS deficiency

with the only disease manifestation being palmar hyperkeratosis and urine organic acids that showed the presence of a few abnormal metabolites. The patient's sister was found to carry the chromosome 21 inversion, which also likely results in a null allele, as well as the p.Cys189Arg variant identified in her mother. The sister's history was normal except for hyperkeratotic skin lesions. Subsequently, enzymatic analysis confirmed mild HLCS deficiency but with no abnormal urine metabolites or lactic acid elevation.

Comparison of the enzymatic activities of all three patients reveals a number of interesting conclusions. The proband's severe clinical presentation is consistent with the significantly decreased activity in all three enzyme complexes. The absence of any appreciable pyruvate carboxylase (PC) activity combined with the "biotin-unresponsive" pathogenic variant likely explains the proband's persistent lactic acid elevations on high dose biotin. The significantly decreased propionyl CoA carboxylase (PCC) activity in the proband's mother compared to the only mildly decreased activity in the proband's sister provides a plausible explanation for the mother's acylcarnitine abnormalities. Interestingly, the patient's sister was found to have the lowest activity of 3-methylcrotonyl-CoA carboxylase when compared to her brother and mother, but with an absence of 3-methylcrotonylglycine in the urine or C5-OH abnormalities on acylcarnitine analysis. The exact reasons for this are uncertain at this point but it has previously been shown that there is known biochemical heterogeneity between patients (Burri et al. 1985).

This case supports the necessity of determining an HLCS patient's molecular diagnosis. If a non- K_m -variant is identified, treating physicians should expect that a patient will only experience therapeutic benefit with a very high biotin dose. In line with this, our patient's case also argues for a revision of how we classify *HLCS* variants and patients. Labeling an HLCS patient and/or an *HLCS* variant as "biotin-unresponsive" may inadvertently cause a patient to miss out on a potentially beneficial medication. As the exact mechanisms for biotin responsiveness have yet to be fully elucidated, an alternative classification is not readily apparent. Our case, in combination with the recent report by Slavin et al. (2014), provides evidence that large doses of biotin can ameliorate some symptoms even when the detected mutations suggest severe disruption in the production of a functional protein. These individuals, however, will require closer observation, especially during periods of stress and illness. Furthermore, supplementary therapies such as carnitine, sodium bicarbonate, and protein restriction may be necessary. Additionally, when standard molecular testing does not reveal an abnormality, an underlying chromosomal rearrangement should be considered.

Take-Home Message

The molecular characterization of patients with holocarboxylase synthetase deficiency is an important aspect of their workup, as it facilitates necessary family testing and provides useful insight into their potential response to biotin therapy.

Details of Contributions of Individual Authors

Shane C. Quinonez: manuscript preparation, Table 1 creation.

Andrea H. Seeley: manuscript preparation, Fig. 1 design, and Table 1 creation.

Thomas W. Glover: cytogenetic laboratory interpretation, Fig. 2 design, and manuscript review.

Cindy Lam: cytogenetic laboratory interpretation and Fig. 2 design.

Bruce A. Barshop: biochemical laboratory interpretation and manuscript review.

Catherine E. Keegan: manuscript review and planning/organization of manuscript.

Manuscript Guarantor

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Compliance with Ethics Guidelines

Shane C. Quinonez declares that he has no conflict of interest.

Andrea H. Seeley declares that she has no conflict of interest.

Thomas W. Glover declares that he has no conflict of interest.

Cindy Lam declares that she has no conflict of interest.

Bruce A. Barshop declares that he has no conflict of interest.

Catherine E. Keegan declares that she has no conflict of interest.

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Details of Ethics Approval

Not required by our institution. Informed consent was obtained from all patients for which potentially identifying information is included in this article.

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