

Homocystinuria in a consanguineous indigenous family from rural Honduras: a ten-year follow up and literature review of familial cases

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How to cite this article: Kodali AT, Schrunder ER, Kennedy LS, et al. Homocystinuria in a consanguineous indigenous family from rural Honduras: a ten-year follow up and literature review of familial cases. *Arch Clin Cases*. 2026;13(1):19-25. doi: 10.22551/2026.50.1301.10336.

ABSTRACT

Homocystinuria (HCU) is a rare autosomal recessive metabolic disorder, characterized by a mutation in the enzyme cystathionine beta-synthase and abnormally high levels of homocysteine in the blood. HCU that runs in a family is rare; prior to this report, there have been only 150 familial cases described in the literature. Here, we describe a familial cluster of HCU in four children in "Family V," a consanguineous indigenous family from rural Honduras with a 10-year clinical follow up. We describe the diagnosis, presentation and progression of three patients who were diagnosed in 2015; critical findings include substantial vision loss in Patients 1 and 2, and a significant decline in language ability in Patient 3. We also describe the presentation of Patient 4, a grandchild who we diagnosed with probable HCU based on symptoms very similar to his siblings and highly suspicious for HCU. Additionally, we completed a narrative review of previously published familial HCU cases, using PubMed and Google Scholar, to highlight common phenotypic trends in familial HCU patients. In the reported familial cases, 57% had CNS complications, 48% had ocular complications, and 30% had cardiovascular complications.

KEYWORDS: Homocystinuria; Cystathionine beta-synthase deficiency; Consanguinity; Familial case series; Rare metabolic disease; Rural healthcare

INTRODUCTION

Homocystinuria (HCU) is an autosomal recessive metabolic disorder caused by mutation in the enzyme cystathionine beta-synthase (CBS), a key protein in the transsulfuration pathway; the result is elevated levels of homocysteine in the blood. HCU can affect the skeletal, nervous, ocular, and vascular systems. Though symptoms vary, it is commonly characterized by nearsightedness, osteoporosis, lens dislocation, higher risk of thromboembolic events, and developmental delays [1]. HCU manifests on a variable timeline – for untreated patients, symptoms may begin around 5 to 7 years old, though some patients appear healthy until onset of symptoms in adulthood [2]. HCU diagnosis requires screening blood plasma for homocysteine or methionine levels. In many clinics, this occurs shortly after birth during routine newborn screening (NBS). If levels are

inappropriately high, treatment should begin immediately with oral pyridoxine, betaine, and a low-methionine diet. If initiated sufficiently early in life, and the patient is responsive, many never develop complications of HCU. If left untreated, HCU symptoms that develop are irreversible.

HCU's worldwide prevalence has been estimated to be from 1 in 200,000 to 1 in 335,000. However, it is likely to be underdiagnosed due to confusion with other, more common conditions. The clinical manifestations of HCU are often nonspecific (including skeletal and muscular deformations and intellectual disability), which can result in misdiagnosis [3]. Diagnosis is especially challenging in low-resource settings and nations without equitable NBS access. In Honduras, a nationwide NBS program was implemented in 2016 with promising results, yet NBS is still not the standard of care for many of the country's most rural and impoverished citizens, which results in underdiagnosis of several congenital conditions, including HCU [4]. NBS access across Latin America is complicated further by difficulties with locating and following up with rural families to discuss

Received: February 2026; Accepted after review: March 2026;
Published: March 2026.



abnormal results, run additional diagnostic tests, detail treatment plans, and provide ongoing monitoring [5].

In 2013, our research team met “Family V,” who reside in a small, highly consanguineous, and impoverished community in rural northwestern Honduras, comprised of members of an indigenous Honduran Tolupan tribal group. They had three children that displayed delayed psychomotor development, marfanoid habitus, lenticular displacement, high-arched palate and incisors, and pale and thin skin. In 2015, alongside collaboration with pathology researchers from Dartmouth’s Geisel School of Medicine, dried blood testing yielded an official diagnosis of HCU [6]. Over the following decade, we have continued to follow up with Family V, including routine checkups and refreshed nutritional supplies. During this time, a four-year-old child grandchild was brought into the household; based on his clinical characteristics of delayed psychomotor development and palatal and dental defects, the team had strong clinical suspicion for HCU.

Here, we aim to highlight the diagnostic challenges of rare metabolic conditions such as homocystinuria (HCU) in rural Honduras and to describe the long-term clinical progression of affected individuals by reporting the familial cluster observed in Family V. Three of the patients described here were previously reported by Turner et al. (2015) [6] in the context of identifying a novel CBS mutation; the present report expands upon that work by providing a 10-year clinical follow-up and a narrative review of previously reported familial homocystinuria cases.

■ CASE PRESENTATION

Señora and Señor V had six living children (Table 1). The family is indigenous. All the children were born to the same mixed-race, consanguineous parents. They were born vaginally, full-term, at home, and with no birthing complications. Señor V succumbed to injuries from an unrelated local dispute. One child died in infancy; the cause of death is unknown. Two daughters are clinically normal. One is the mother of a child presumed to have HCU based on differential diagnosis (Señora V’s first grandchild, aka Patient 4).

Patient 1

Patient 1 was diagnosed at 14 years of age in 2015. According to her mother, she demonstrated delayed psychomotor development that began between 1-5 years of age, including a difficulty acquiring both language and fine motor skills relative to developmental expectations. Throughout childhood, motor coordination remained impaired. She had also had progressive vision loss.

At the time of diagnosis, the patient presented with progressive musculoskeletal and craniofacial abnormalities. Physical examination revealed marfanoid habitus, including

elongated limbs and generalized joint hypermobility involving the elbows, knees, and ankles. She had severe scoliosis and had become almost entirely wheelchair-bound due to progressive motor limitations. Craniofacial findings included a markedly pointed chin and an ogival palate. She was beginning to lose several maxillary teeth. Additional findings included very thin, black hair with weak implantation.

Using penlight evaluation and pupillary dilation in her home, lenticular displacement was evident, and vision testing revealed substantial deficits. Additional findings included very thin, black hair with weak follicular implantation. Neurological examination demonstrated difficulty executing fine motor movements, hypotonia, and muscle weakness in all four limbs.

The patient is currently 24 years old. Over time, with treatment with vitamin B6 and improved nutrition and medical support (more details below), some functional improvement in muscle tone and motor skills has been observed. Although she continues to rely primarily on a wheelchair for mobility, she is intermittently able to ambulate short distances for up to 5 minutes without wheelchair assistance. Her lenticular dislocation has progressed to complete lens dislocation, and she is now completely blind (Figure 1)

Patient 2

Patient 2, the proband, was diagnosed at 11 years of age in 2015 (note that Turner et al. (6) previously misreported Patient 1 as the proband because all children’s DNA reached the laboratory at the same time). During early childhood, his mother noted that he had delayed psychomotor development, particularly in language acquisition and fine motor skills.

At the time of diagnosis, physical examination revealed an elongated, asymmetric body habitus with marfanoid features and a thin build. Craniofacial and oral examination demonstrated a high-arched palate and crowded dentition, with stacking of canines and molars in the upper jaw. Additional findings included very fine black hair with weak follicular implantation and thin skin with prominent striae across the abdomen. Ophthalmologic evaluation with penlight and dilation identified early lenticular displacement. Neurologically, the patient exhibited neurodevelopmental delay but retained the ability to speak.

The patient is currently 21 years old. Overtime, the patient experienced progressive ocular involvement, ultimately resulting in complete lens dislocation and blindness. Cognitive impairment has progressively worsened, accompanied by intermittent mood disturbances characterized by episodes of anger. Despite these neurological changes, with vitamin supplementation, the patient has retained the ability to walk

Table 1. Family V.’s children description.

Case Report Designation	Relationship to Mother and Father V.	Current age	Health	HCU and Dx method
Patient 1	First daughter	25	HCU	2015, by molecular pathology
Patient 2	First son	22	HCU	2015, by molecular pathology
N/A	Second daughter	Unknown	Normal	Normal appearance
N/A	Third daughter	Unknown	Normal	Normal appearance
Patient 3	Fourth daughter	15	HCU	2015, by molecular pathology
N/A	Second son (died in infancy)	Deceased	Unknown	Not tested
Patient 4	Grandson (son of third daughter – father unknown)	4	HCU	2023, by differential diagnosis



Fig. 1. Patient 1 – She is mostly wheelchair bound and needs assistance to hold her head straight. However, she can leave her wheelchair and stand, with support. Her speech is limited to simple requests and responses.

independently, and some fine motor skills have improved, including the ability to pick up and manipulate objects (Figure 2).

Patient 3

Patient 3 was diagnosed at 4 years of age in 2015. According to her mother, the patient did not crawl or walk until approximately two years of age, suggesting early motor developmental delay.

At the time of diagnosis, physical examination revealed marfanoid habitus, including a long face, prognathism, thin build and scoliosis. The patient had long, slender limbs with arachnodactyly and elongated digits of the hands and feet. Oral examination demonstrated an ogival palate. Additional findings included hypopigmented skin and very thin dark hair with weak follicular implantation. Neurological evaluation revealed difficulty pronouncing words and impaired fine motor coordination.

She is currently 14 years old. Over the subsequent 10 years, the patient experienced progressive decline in language abilities. Motor function has also deteriorated, with increasing difficulty standing independently; however, she has retained the ability to move independently, suggesting partial preservation of gross motor function. Her vision is normal, and no lens dislocation has been detected via at-home ophthalmologic evaluation (Figure 3)

Patient 4

The fourth patient is a 4-year-old boy. He is a grandson who was born after the molecular diagnoses of Patients 1, 2, and 3. He has visible signs of delayed psychomotor development, particularly in language, as he cannot articulate speech beyond small words; he has macroglossia, which



Fig. 2. Patient 2 – He can walk without assistance; he speaks in a limited way and communicated with the care team. During our visit, he was unwilling to undergo a full clinical examination.

may contribute to his difficulty with language. He has bilateral valgus foot and is unable to stand or walk independently. In the mouth, in addition to macroglossia, he has an ogival palate, and stacked incisors, canines and molars, and was missing 2 teeth. He has thin hair that was implanted well; his skin was of normal thickness and elasticity. Ophthalmological evaluation showed visual acuity. Neurological examination revealed some hypotonia (Figure 4).

The diagnosis of HCU is currently based on clinical suspicion and familial history, as molecular testing has not been performed due to limited financial resources. Because of the patient's young age, long-term progression data are not yet available

■ SUMMARY OF DIAGNOSIS

ACTS Honduras partnered with the molecular pathology research team at Dartmouth's Geisel School of Medicine to diagnose patients 1, 2, and 3 via molecular and blood testing. The detailed methodology is available in Turner et al. [6]. Though whole blood testing was ideal, collecting and transporting samples caused several challenges due to the remote location of Family V's community and distance from the nearest hospital and testing facility. In 2014, the team collected buccal swabs with DNA from 6 members of Family V and 29 adults and children living in the small village (note that Turner et al. [6] reported the number of additional community members as 35 due to an error in record keeping); they also collected dried blood samples for



Fig. 3. Patient 3 – She was able to walk and stand, sometimes needing to lean on walls for support. She has an extremely thin and long build.



Fig. 4. Patient 4 – He was unable to stand without support and typically moves by crawling. His macroglossia is also visible.

Table 2. Pre- and post-treatment homocysteine levels.

Patient	Pre-treatment	Post-treatment	% change
Patient 1	187.0 nmol/ml	162.7 nmol/ml	-13.9%
Patient 2	193.3 nmol/ml	150.3 nmol/ml	-25.0%
Patient 3	121.5* nmol/ml	158.9 nmol/ml	+26.7%

*Patient 3’s initial sample collection had substantial potential for contamination due to the difficulties with collection.
Reference value - < 15.0 nmol/ml.

homocysteine testing, both of which bypassed the logistical challenges of whole blood.

Genetic testing was performed using whole-exome sequencing. A multi-step filtering strategy and phenotype-driven gene prioritization identified a novel c.921delC variant in the cystathionine beta synthase (CBS) gene, resulting in a missense mutation (p.Tyr308Thrfs*11). Patients 1, 2 and 3 were all homozygous for this mutation, and their mother was heterozygous. The variant causes a frameshift of the CBS transcript with a premature stop codon 11 amino acids downstream of the mutation, resulting in a truncated CBS protein with loss of normal enzymatic function and potentially also causes nonsense-mediated mRNA decay, lowering the amount of CBS translated. Dried blood spot analysis confirmed substantial homocysteine levels in Patients 1, 2 and 3 (Table 2) [6].

The combination of mutation and blood homocysteine levels confirmed the diagnosis of homocystinuria. A standard treatment of daily vitamin B6 (pyridoxine) supplementation was started. However, all three patients did not have significantly reduced homocysteine levels after 12 weeks of treatment, indicating that the patients were pyridoxine-nonresponsive (Table 2). The lack of responsivity is seemingly in line with the severely truncated CBS protein resulting from the patients’ mutation [6].

Therefore, the patients were switched to a daily multi-vitamin and vitamin B12 supplementation, as well as monthly food and nutrition support.

LITERATURE REVIEW

We performed a narrative review of the literature on familial cases of HCU using the key phrase “familial homocystinuria” in PubMed and Google Scholar databases. All manuscript full texts were screened to ensure one or multiple descriptions of HCU in a family setting (parent/children, sibling, cousin, etc.); any article that did not explicitly note familial HCU were excluded. The search spanned all published articles in PubMed and Google Scholar until March 15, 2025. All articles that were written in a language other than English or Spanish were translated using Google Translate; therefore, there may be slight errors with the original reports. We found 66 manuscripts that fit our criterion, with a total of 154 individual patient cases (including the four patients that we report here). The complete dataset of previously reported familial cases is provided in Supplementary Table S1 and summarized in Table 3.

Our review found that, of the 154 familial cases found, 59.1% (n=91) were B6-responsive. 23.4% (n=36) were B6-nonresponsive, including the four patients described in this report (the other 27 patients were either unknown or had a variant of HCU).

Table 3. Summary of literature review.

Sex Ratio	Median age (range)	Geography [†]	HCU Type [‡]	Consanguinity	Cardiovascular manifestations [§]	Ocular manifestations [§]	CNS manifestations [§]	Other manifestations [§]
0.78	14.4 (newborn – 67)	Western Europe – 24.7% (n=38) South Asia – 19.5% (n=30) Eastern Europe – 14.3% (n=22) North America – 11.7% (n=18) East Asia – 11.7% (n=18) North Africa – 8.4% (n=13) West Asia – 5.8% (n=9) Central America – 2.6% (n=4) Oceania – 1.3% (n=2)	B6-responsive – 59.1% (n=91) B6-non responsive – 23.4% (n=36) cblC disease – 1.9% (n=3) cblG disease – 1.3% (n=2) Unknown – 14.3% (n=22)	Non-consanguineous – 33.8% (n=52) Consanguineous – 27.9% (n=43) Unknown – 38.3% (n=59)	Total, cardiovascular manifestations – 29.9% (n=46) Deep vein thrombosis – 32.6% (n=15) Thrombosis – 15.2% (n=9) Anemia – 10.9% (n=7) Ischemia – 8.7% (n=4) Embolism – 8.7% (n=4) Mitral valve prolapse – 8.7% (n=4)	Total, ocular manifestations – 48.7% (n=75) Lens displacement – 29.3% (n=22) Myopia – 28.0% (n=28) Lens dislocation – 25.3% (n=19) Lens subluxation – 20.0% (n=15) Glaucoma – 14.7% (n=11) Cataract – 8.0% (n=6)	Total, CNS manifestations – 57.1% (n=88) Intellectual disability – 44.3% (n=39) Delayed psychomotor development – 29.5% (n=26) Seizure, spasms, or tremors – 21.6% (n=19) Movement disorder – 21.6% (n=19) Abnormal brain structure – 13.6% (n=12) Speech impairment – 12.5% (n=11) Muscle weakness – 12.5% (n=11) Behavioral impairment – 11.4% (n=10) Primitive reflexes – 9.1% (n=8) Attention deficit or hyperactivity – 5.7% (n=5)	Total, other manifestations – 46.8% (n=72) Marfanoid characteristics – 38.9% (n=28) Osteoporosis – 18.1% (n=13) Arachnoidactyly – 16.7% (n=12) Chest deformities – 15.3% (n=11) Valgus knee – 15.3% (n=11) Scoliosis – 12.5% (n=9) Arched palate – 12.5% (n=9) Hypotonia – 11.1% (n=8) Skin or hair dyschromia – 6.9% (n=5) Respiratory symptoms – 6.9% (n=5)

[†] = If geography was not explicitly noted, first author affiliation was used as an approximation.

[‡] = cblC and cblG disease were included due to the similarities with classic homocystinuria.

[§] = "Total" percentage of patients with type of manifestation was taken from total pool of 154. Individual manifestations were taken from the manifestation-specific pool (e.g., "Deep vein thrombosis – 32.6%" represents the 15 / 46 patients with any cardiovascular manifestations).

One striking feature of HCU is deformities in connective and skeletomuscular tissues. Of familial cases in our review, 18% (n=28) had Marfanoid characteristics: 8.4% (n=13) had osteoporosis, 7.8% (n=12) had arachnodactyly, 7.1% (n=11) had chest deformities, 7.1% (n=11) had valgus knee, 5.8% (n=9) had scoliosis, and 5.8% (n=9) had an arched palate, and 5.2% (n=8) of patients had hypotonia. Our four patients fit the connective and skeletomuscular profile. Patients 1, 2, and 3 have Marfanoid characteristics. Patient 1 has scoliosis, joint hypermobility, and an ogival palate. Patient 2 has a long, thin build and a high arched palate with crowded teeth. Patient 3 has a long, thin build, scoliosis, and arachnodactyly. Patient 4 is quite young and has been treated for years with B6; his build is apparently more normal than his affected family members. He has some physical deformities, including an ogival palate, stacked incisors, and bilateral valgus foot.

Additionally, ocular complications are common in HCU patients. From our review, we found nearly half (48.7%, n=75) of familial HCU patients had ocular manifestations. Lens displacement (14.3%, n=22), myopia (13.6%, n=21), complete lens dislocation (12%, n=19), and lens subluxation (10%, n=15) were common in familial cases. Patients 1 and 2 were diagnosed with lenticular displacement a decade ago, and their visual acuity has progressively worsened over the years. Based on an assessment for visual acuity and external examination Patients 3 and 4 are seemingly free of any ocular complications but are relatively young in terms of disease progression; the team was also not able to do a full retinal exam and thus would not have been able to see signs of internal degradation or changes.

Homocysteine accumulation in the blood can also cause substantial toxicity to the central nervous system. There are a wide range of potential impacts. In our review, 57.7% (n=88) of patients had a CNS manifestation. 25.3% (n=39) of the 154 patients with familial HCU suffered from intellectual disability, ranging from moderate to severe. 16.9% (n=26) had delayed psychomotor development as infants and young children. 12.3% (n=19) suffered from some kind of seizure or tremor disorder, and another 12.3% (n=19) had a movement disorder. 7.8% (n=12) had impacted brain structure, including issues with white matter development. 7.1% (n=11) had impaired speech. Lastly, 7.1% (n=11) had muscle weakness. All four of the patients reported here had delayed psychomotor development, with varying impacts. Patients 1 and 2 struggled to pick up language and fine motor skills, though Patient 2 can articulate some complete sentences and communicate with adults. Patient 3 was substantially delayed in crawling, then walking, and still struggles to move. Patient 4 substantially struggled with language development and walking, due to bilateral valgus foot; he is able to crawl.

HCU is associated with striking patterns of cardiovascular pathology. In our review of familial HCU patients, about 30% (n=46) had a cardiovascular manifestation. 9.7% of patients (n=15) had deep vein thrombosis, and 5.8% (n=9) had thrombosis or thrombotic events. 4.5% (n=7) suffered from ischemia, 3.2% (n=5) suffered from stroke, and 2.6% (n=4) had experienced mitral valve prolapse. Vascular events are the largest driver of HCU-related mortality; nearly half of untreated HCU patients have vascular events by the age of 30 [7]. The patients we report in Family V have not suffered any major cardiovascular events.

Lastly, our literature review yielded five other papers that described a family with four or more cases of HCU [8–12].

Family V, as well as the families described in Waheed et al., and Kluijtmans et al., are classified as highly consanguineous [8,9]. These reports add to the literature identifying HCU's autosomal recessive inheritance pattern and the devastating impact undiagnosed and untreated HCU can have on rural, impoverished families. Indeed, of the 95 familial cases where consanguinity was explicitly noted in our review, 45.3% (n=43) were from consanguineous families. Parental consanguinity is known to drive rates of recessive genetic disorders, like HCU, but addressing the problem is difficult. In communities like Family V's, where the tiny population is ethnically homogenous and isolated, options for non-related partners are limited [13]. Families also lack access to genetic counseling, ultimately driving the risk of autosomal recessive disease in younger generations.

■ DISCUSSION

Homocystinuria (HCU) is a rare, congenital metabolic disorder of the methionine cycle. Here, we describe four children with HCU who came from Family V, a consanguineous indigenous Honduran family residing in a rural village in Honduras. Our group originally diagnosed Patients 1, 2, and 3 through clinic outreach to the community in 2015. In the years since the original diagnosis, we diagnosed their younger grandsibling, as well.

HCU is characterized by deficiency of the enzyme cystathionine β -synthase (CBS), a crucial transsulfuration enzyme in the methionine cycle. There are two phenotypic forms of classical HCU, B6-responsive and non-responsive, which correlate with CBS mutation genotype. In B6-responsive homocystinuria, CBS mutants have a reduced but moderate affinity for pyridoxine and supplementation can increase intracellular pyridoxine levels enough to treat homocystinuria phenotype; B6 non-responsive patients have mutations that dramatically reduce pyridoxine affinity so that supplementation cannot overcome the defect [14]. B6 non-responsiveness is associated with worse outcomes and earlier onset.

The ultimate goal of treatment for HCU under current guidelines is to reduce plasma homocysteine concentrations. For B6 responsive patients, the guidelines suggest 300–600 mg/day of pyridoxine and folate and vitamin B12 supplementation. For B6 non-responsive patients, the guidelines suggest more intensive care, with a methionine-restricted diet, folate and vitamin B12 supplementation, cysteine supplementation, and betaine [15].

There are several barriers in place to treatment of patients with HCU in global, rural, and underserved communities, like Family V's. NBS access is uneven across Latin America, and Honduras still has limited systematic access to NBS. Barriers range from a shortage of specialists in metabolic disorders, limited healthcare and laboratory infrastructure, geographic challenges in transporting samples, and more [16]. Therefore, diagnosis is often limited to clinical suspicion, and subsequent provision of treatment and follow-up testing is difficult.

■ CONCLUSION

The Family V case highlights the complexity of providing medical diagnosis, care, and education in Honduras's most remote and impoverished villages. More research about access to screening, family planning counseling, and options

for complex diagnosis in remote communities are crucial to improve access to quality care in the nation's most underserved communities.

Source of funding

We acknowledge funding from Dartmouth Cancer Center of Dartmouth Geisel School of Medicine and Dartmouth Health, which gets support from the US National Cancer Institute grant P30CA023108. The funders had no role in study design, data collection, analysis, or manuscript preparation.

Statement of Consent

The patients' mother provided signed consent and approval to document her children's cases and photos in a publication.

Data sharing statement

Not applicable

Acknowledgments

We thank Family V, for working with us on diagnostic and treatment methods over the years and for allowing us to report their case in a publication; the local Health and Development community committee, for facilitating our meetings and for providing care, food, and assistance to the family; Suzanne Burgos PA, for providing care to Family V for over a decade and for giving clinical guidance for our report; Gregory Tsongalis PhD and Joel Lefferts PhD, for leading the diagnosis of HCU in Family V; Dean Seibert MD, for leading the early efforts to provide treatment and determine the cause of symptoms; and Steven Fiering PhD, for mentoring research among the Dartmouth Cancer Scholars and reviewing our manuscript.

Potential Conflicts of Interest

Anahita Kodali, Linda Kennedy, and César Ulises Alas Pineda serve as unpaid steering committee members of ACTS Honduras, the NGO that first met Family V and has coordinated their care since their original diagnosis in 2015.

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