Nephropathic cystinosis in a Chilean cohort: Clinical and genetic characterization

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Abstract

Cystinosis is a rare disease caused by *CTNS* gene defects. The main clinical presentations are nephropathic infantile cystinosis (NIC) and nephropathic juvenile cystinosis (NJC); both develop chronic kidney disease (CKD) and extrarenal complications. Opportune diagnosis and access to therapy are challenging in developing countries. Objectives: To describe the clinical and genetic profile of all cystinosis patients diagnosed in Chile. Methods: We performed a retrospective review of the clinical records of cystinosis patients diagnosed from 1994 to 2022. Age at diagnosis, glomerular filtration rate, metabolic variables, anthropometric values, treatment, genetics analysis and outcomes were recorded. Results: Nine patients (8NIC/1NJC) were diagnosed. Patients with NIC had a median age of 16.5 (IQR 13-23) months at diagnosis, and two patients died during follow-up. Most patients started cysteamine therapy within 5 months after diagnosis and reached CKD stages 3-4 within four years. Laboratory and clinical evaluations improved after CKD management and cysteamine therapy. During the follow-ups, all but one of the NIC patients showed height for age Z-score values between -1.5 and -4.0. Two patients received kidney transplantation, and one of them still remains functional after 15 years. The single NJC was a 21-year-old female patient who received insufficient cysteamine and rapidly reached CKD stage 4. Genetic testing was positive in 7/7 cases, with del57kb being the predominant variant (10/14 alleles). Conclusion: Developing countries still face many challenges in providing adequate healthcare to cystinosis patients. Opportune genetic testing may facilitate early diagnosis, resulting in better prognoses.

Introduction

Cystinosis is an autosomal recessive disease associated with biallelic *CTNS* variants (MIM#606272) that encode the cystinosin protein. This protein acts as a lysosomal transporter that is defective in patients with cystinosis causing cystine accumulation throughout multiple organs and their progressive deterioration [1, 2].

Cystinosis affects 1 in 100,000-200,000 individuals with varying clinical manifestations depending on the disease onset and severity [3, 4]. Nephropathic infantile cystinosis (NIC; OMIM#219800) is the predominant clinical form, presenting symptoms within the first months of life. This clinical form is the most severe and eventually progresses to chronic kidney disease (CKD) during the first decade of life, often requiring kidney replacement therapy (KRT). A kidney transplant (KT) is usually required without evidence of recurrence in allografts. KRT and the involvement of other organs can be delayed with optimal clinical management [5, 6]. Nephropathic juvenile cystinosis (NJC; OMIM#219900) is characterized by late-onset of symptoms, typically during adolescence, and together with NIC is diagnosed in 95% of all cases. NJC patients require KRT later in life compared to NIC patients.

Traditionally, NIC/NJC is diagnosed by measuring intra-leukocyte cystine, but it is not usually available in developing countries and genetic testing has evolved as a feasible diagnostic tool. Genetic diagnosis yields a mutation detection rate > 95% and has a broad spectrum of *CTNS* variants [7]. More than 150 variants have been identified, but a 57-kb deletion (del57kb) involving a major portion from *CTNS* is the most common variant identified in patients from Europe and North America, with a lower frequency in the Middle East [8].

Cysteamine is the only drug available to improve renal and extrarenal prognosis [9]. Opportune diagnosis and treatment with cysteamine are still challenging in some countries since the disorder is infrequent, and physicians lack experience in achieving adequate management of these patients. Additionally, bad outcomes are exacerbated due to constrained financial resources and/or unequal drug distribution, evidencing the significant gap between developing and developed nations in terms of the clinical evolution of these patients [10, 11].

We aimed to describe clinical, genetic and social determinants related to therapy and their long-term follow-up in all Chilean cystinosis patients known to be diagnosed in the last 27 years.

Methods

We conducted a retrospective review of the clinical records, genetic analysis and specific social determinants in 9 cystinosis patients known to be diagnosed in Chile between 1994 and March 2022. We analyzed characteristics at disease onset to classify each patient as NIC or NJC, annual monitoring of biochemical variables [serum creatinine, calcium, phosphorus and plasma bicarbonate, intact parathyroid hormone (iPTH), free thyroxine, thyroid-stimulating hormone, proteinuria], recombinant human

growth hormone (rhGH) use and anthropometric values according to World Health Organization/Centers for Disease Control and Prevention. In addition, other complications were registered: corneal crystals, exocrine or endocrine dysfunction, myopathies, neurocognitive impairment, swallowing difficulties and bone mineral disturbances. Conditions at the time of recruitment were registered as alive or deceased, with or without KT. Glomerular filtration rate (eGFR) was estimated using Schwartz's formula until 16 years of age and the CKD-EPI equation in older patients.

Regarding cysteamine treatment for each patient, we registered their health system (public vs. private) and funding sources. To estimate if treatment was sufficient or insufficient, we evaluated the time between the NIC/NJC diagnosis and access to the first dose of cysteamine. The cysteamine dose was adjusted to body surface area during clinical follow-up and the use of cysteamine eye drops was also registered.

Genetic testing was carried out in blood samples from 7 patients and 9 relatives collected between 2016 and March 2022, all declaring themselves to be Chileans. For genotyping, DNA was isolated using the Whole Blood Genomic DNA Purification kit (ThermoFisher®). Firstly, the specific del57kb PCR was performed in all samples with LDM/D17S829 primers [12]. Two patients with negative results for the del57kb were considered for a posterior analysis in a Genetic Analyzer ABI 3500 (Applied Biosystems) by direct sequencing on the *CTNS* coding exons (exons 3–12). Sequence analysis was performed using the SeqScape v2.5 software to align the obtained sequences with the reference sequence NM_001031681.2. We checked if the detected variants were present in databases (HGMD, ClinVar) and analyzed them with the predictive bioinformatic tools (Mutation taster, SIFT and Polyphen-2). For each variant, segregation analysis was performed in the family by targeted analysis, LDM/D17S829 PCR or exon sequencing, to establish inheritance and/or to provide genetic counseling if requested.

Statistical Analysis

Continuous variables are presented as medians and ranges. Qualitative variables are presented as rates or percentages.

Ethics Concerns

Ethical approval was obtained from the corresponding Institutional Review Board and local Hospital Ethics Committee. This study was performed following the Helsinki Declaration, Good Clinical Practice and Chilean Legislation (Laws nr. 20.120, 20.584 and 19.628). All legal guardians of pediatric patients and adult participants signed an informed written consent agreeing to be included in this study for retrospective data collection and to provide a blood sample for genetic analysis.

Results

Nine patients with cystinosis diagnosed between 1994 and March 2022 at Chilean nephrology units were included in this study. Basic clinical characteristics and genetic findings are described in Table 1. The diagnosis of 8 cases was NIC at a median age of 16.5 (IQR, 13–23) months. The single NJC case (P8) was a 21-years old female patient first diagnosed by an ophthalmologist with corneal deposits, and later received a nephrological evaluation which revealed she had CKD stage 4.

Table 1
Basic clinical and genetic characteristics of the patients diagnosed with NIC or NJC

Patient (sex)	Clinical Diagnosis	Age at Diagnosis	Height / Age Z score at diagnosis[b]	Follow-up (years)	Current condition	Cysteamine therapy	Last CrCl (ml/min/1.73)	Genotype
P1 (M)	NIC	7 mo	ND	1	Deceased at 20 mo	According to consensus[b]	0.73 mg/dL (creatinine)[c]	ND
P2 (F)	NIC	6 mo	<-2.0	27	Deceased at 28 y.o.	Insufficient	25.6 (KT at 6 y.o.)	ND
P3 (M)	NIC	14 mo	ND	25	Cysteamine-treated	Insufficient	139 (KT at 10 y.o.)	[g.del57kb] [g.del57kb]
P4 (M)	NIC	23 mo	-3.32	13	Cysteamine-treated	According to consensus[b]	37.4	[c.992_993insG] [c.992_993insG]
P5 (F)[a]	NIC	13 mo	-1.34	8	Cysteamine-treated	According to consensus[b]	24	[g.del57kb] [g.del57kb]
P6 (F)[a]	NIC	11 mo	0.21	6	Cysteamine-treated	According to consensus[b]	51	[g.del57kb] [g.del57kb]
P7 (F)	NIC	12 mo	-2.46	5	Cysteamine-treated	According to consensus[b]	35	[g.del57kb] [g.del57kb]
P8 (F)	NJC	21 y.o.	-3.03	0.8	Cysteamine-treated	Insufficient[b]	14.4	[c.416C > T] [c.416C > T]
P9 (F)	NIC	28 mo	-4.29	0.1	Recently diagnosed	According to consensus[b]	56	[g.del57kb] [g.del57kb]

NIC, nephropathic infantile cystinosis. NJC, nephropathic juvenile cystinosis. ND, not determined. KT, kidney transplant.

[a] These patients were siblings.

[b] Consensus describes cysteamine therapy as 1.30 g/m2/day for children < 12 years and 2 g/day for patients > 12 years if weight is > 50 kg, divided 4 times each day.

The two NIC patients diagnosed before 2000 died during the follow-up; the first patient (P1) died when he was 20-months old after an abdominal shock, while the second patient (P2) died when she was 28 years old after respiratory failure due to lung disease.

Figure 1 shows the eGFR of 7 out of the 8 NIC patients throughout their follow-ups to date or until they deceased. Patient (P1) is not shown in the figure, because some data were not available.

Patient P2 started peritoneal dialysis when she was 3 years old and received a kidney allograft from a living-related donor at the age of 6, followed by a decline of allograft function not related to cystinosis disease. During her life, she had restricted and irregular access to cysteamine therapy and developed multi-organic complications related to cystinosis. Patient P3 is a 26-year-old male patient who underwent KT at 10 years of age and currently has normal creatinine clearance.

At the last visit, the remaining five NIC living patients were classified in CKD stages 3–4. However, two siblings (P5 and P6) showed normal kidney function at the beginning of the follow-up and underwent a progressive decline. Patient (P7) showed an eGFR of 27

ml/min/1.73m2 at the time of diagnosis that improved slightly after starting cysteamine therapy. Patient 9 (P9) was diagnosed recently, therefore, only her initial evaluation is shown.

As eGFR declines, proteinuria and tubular losses decrease. Consequently, we registered lower requirements of oral supplements to replace losses of Fanconi's tubulopathy.

The single NJC patient received insufficient cysteamine therapy and reached CKD stage 5 less than one year after diagnosis.

All patients had hypophosphatemia and four had high iPTH based on their CKD stage at diagnosis. All patients presented proximal tubulopathy requiring high sodium bicarbonate supplementation of up to 36 grams per day. All non-transplanted patients required permanent bicarbonate supplementation during the entire follow-up period. When tubulopathy and CKD treatments were provided, all patients improved their clinical and biochemical values.

Regarding extrarenal manifestations, five patients developed hypothyroidism requiring levothyroxine treatment. All patients developed ocular involvement with corneal deposits of cystine crystals and started pharmacy-prepared cysteamine drops as soon as it was diagnosed. Seven patients had photophobia which improved in one of them after KT. Three patients (P2, P3 and P4) that had been monitored for more than 10 years developed other extrarenal complications such as central nervous system involvement, myopathies, swallowing difficulties, hypogonadism and diabetes mellitus.

The median time elapsed between suspicion based on clinical features to a primary diagnosis of cystinosis was 6.5 (range 1 to 10) months, while the posterior median time elapsed until cysteamine oral administration was 2 months. Patient P2 diagnosed in 1997 was late to obtain cysteamine access at 7 years old, while the last two NIC diagnosed patients (P7 and P9) started therapy 1–2 months after diagnosis.

Three patients received insufficient treatment (P2, P3 and P8) in the early stages. The other 6 patients received therapy according to consensus although they had difficulties accessing cysteamine because there was inadequate support from the Chilean health system.

Figure 2 shows NIC patients' height-for-age Z-scores throughout their follow-ups. Only one patient had a normal Z-score and five had Z-scores below − 2.0 at the time of diagnosis. Three patients (P3, P4 and P7) improved their height during the first three years after diagnosis, but later two of them (P3 and P4) deteriorated over time. In contrast, siblings P5 and P6 showed initial Z-scores close to normal limits and although they had access to cysteamine therapy their Z-scores worsened in the following years. The use of rhGH was prescribed to three patients between 7 and 9 years of age, however one of these patients (P6) has not been yet able to start.

Genetic analysis was performed in 7 out of the 9 patients, given that 2 patients died before the implementation of routine molecular diagnostic methods. The genetic analysis confirmed a NIC or NJC diagnosis in all cases, giving a mutation detection rate of 100%. In the first approach to test the presence of the del57kb mutation, 5/7 (71%) patients were homozygous del57kb carriers (Table 1). Figure 3 shows the result of the del57kb analysis in P9, her parents, as well as internal controls.

The two remaining patients required sequencing of the *CTNS* coding exons. Patient P4 is a male with a homozygous genetic nucleotide insertion in exon 12 (c.992_993insG) that predicts a reading frame disruption in the last amino acids (p.Asp332ArgfsX33), yielding a protein slightly shorter than the normal. At the age of 2, his intra-leukocyte cystine quantification performed at Necker Enfants Malades Hospital (Paris, France) resulting in 2,6 nmol cystine/mg protein (normal values are below 0,2).

Patient P8, diagnosed with NJC in adulthood, carried a homozygous single nucleotide substitution in exon 7 (c.416C > T) that predicted an amino acid substitution (p.Ser139Phe) and was previously described in other NJC cases with functional assays describing abolished cystine transport (Fig. 4).

Overall, only four NIC patients had intra-leukocyte cystine quantification and their results showed values above the cut-off point confirming the diagnosis.

Discussion

To the best of our knowledge, this is the first report to describe the clinical and genetic characteristics of nephropathic cystinosis patients in a Latin American country with their long-term follow-up. We registered 9 patients diagnosed in the last 27 years, which was less than expected based on the birth rate in Chile during this period. Misdiagnosis or underdiagnosis cannot be ruled out since the predominant infantile clinical presentation is characterized by a silent period during gestation and even during the first semester of life. Additionally, physicians often lack the experience to perform diagnosis and clinical management.

Our data shows a nephropathic cystinosis prevalence of 0.36 per million people in Chile. The reported worldwide incidence rate is 1 in 100,000-200,000 live births, and its prevalence is approximately 1.6 per million people. This lower prevalence could be due to underdiagnosis or fewer carriers of *CTNS* defective alleles in the Chilean population [4, 13, 14].

The median age at diagnosis of our NIC cases was 16.5 months, ranging from 6 months to 2.3 years, similar to the results in other developing or developed countries [11]. The single NJC case was a 21-year-old woman diagnosed by an ophthalmologist, and a subsequent evaluation showed she had CKD stage 4, suggesting cystinosis might have started during adolescence without evident symptoms.

Our patients received a late diagnosis, which is partly explained by the late appearance of symptoms that usually appear after six months of age despite prior cystine accumulation during gestation. Early detection and treatment are critical in slowing the development and progression of symptoms associated with cystinosis. If treatment is started immediately after birth, progression might be reduced or even prevented [14, 15]. Therefore, the most cost-efficient approach to prevent the multi-organ damage secondary to cystinosis might be to diagnose it as part of a newborn screening program, similar to that recently reported by German research groups [16, 17]. Limited financial resources in developing countries still restrict next-generation sequencing approaches even though they represent an excellent chance to improve outcomes in patients with medically-actionable genetic conditions [18].

Regarding the clinical phenotype in NIC patients, we first observed laboratory and clinical findings associated with Fanconi's tubulopathy and variable initial eGFR that fell to values below 50 ml/min/1.73m2 within the first four years after diagnosis and then remained between 25 and 50 ml/min/1.73m2. Due to the drop in eGFR, proteinuria and tubular losses decrease, and therefore the requirements for oral supplements to replace losses of Fanconi's tubulopathy also decrease.

Two of the patients diagnosed before 2000 had significant difficulties establishing their diagnosis and receiving cysteamine, resulting in a worse evolution, requiring KT in the first decade after diagnosis, possibly related to a lack of medication or intermittent administration. In contrast, the last two NIC patients to be diagnosed had an early genetic diagnosis. In their short-term follow-up, they both had a stable eGFR, and p7 showed a slight improvement from CKD stage 4 to 3 after 5 years of cysteamine treatment. The drop in eGFR in the remaining patients within the first years of follow-up drew our attention; even patient P5, who had prompt access to cysteamine since she was the younger sister of patient P6, diagnosed one year before. This could be a consequence of non-adherence since drug tolerance was suboptimal for these siblings whose mother reported a high frequency of vomiting. Gastrostomy was recommended, but the family rejected the procedure.

All patients had bone mineral abnormalities at diagnoses, such as increased PTH levels and hypophosphatemia; however, all improved at least partially after CKD management. Extrarenal manifestations such as hypothyroidism, hypogonadism, central nervous system involvement, myopathies, swallowing difficulties, and diabetes mellitus were infrequent in our cohort or were observed only in patients at more advanced ages and disease stages.

We observed ocular involvement in all patients with corneal deposits of cystine crystals or photophobia; consequently, cysteamine eye drops were recommended. However, we did not observe a substantial improvement, possibly due to a lack of commercially available eye drops in Chile. Therefore, parents request their preparation with prescription formulas in pharmacies without any regulation to assure their quality and effectiveness.

Growth impairment is frequently observed in cystinosis because of tubulopathy losses. Our patients' Z-scores were severely impacted as CKD progressed, including those cases provided with rhGH. Patient 4 presented hypogonadism that could have

interfered with growth and muscle mass gain, among other metabolic alterations, despite using rhGH. Patient P6 has not been able to initiate rhGH 6 months after its medical recommendation due to a lack of financial support.

Previous reviews from Ariceta in 2015 and Topaloglu in 2021 describe a similar clinical course of cystinosis to the cases reported here [8, 19].

Graft survival of kidney transplantation was good, and recurrence was not observed. One of our patients is a 26-years old male who underwent KT when he was 10 and to date still has normal creatinine clearance.

Digestive losses represent a high risk of morbidity and mortality in cystinosis patients who are highly dependent on the oral intake of supplements and medications to maintain their fluid homeostasis, electrolyte and acid-base balance. Severe gastrointestinal episodes lead to the risk of shock and death, as observed in patient P1 diagnosed in 1997. Patient P2 underwent peritoneal dialysis and KT in her early childhood but suffered a decline in allograft function not related to cystinosis disease. She had insufficient cysteamine therapy during her life, which might have contributed to the development of multi-organic complications associated with cystinosis.

Cysteamine therapy is not commercially available in Chile and the health system does not finance it. As occurs with other orphan drugs, cysteamine is imported as an individualized request, increasing therapy costs. Furthermore, cysteamine has a financial cost of approximately 1.5 times the Chilean minimum wage, resulting in restrictive access to treatment for most of the patient's families. Access to therapy is achieved after requesting it through legal channels in courts of justice; in the meantime, other families supply the treatments while waiting for the Chilean state or private insurance health system to finance it.

Over the last 23 years, most patients started oral cysteamine less than 12–13 months after initiating legal actions. However, donations and solidarity from other families partially supply the drug requirements in the meantime. The period without therapy might increase cystine lysosomal accumulation and damage to their kidneys and eyes, as these are the first organs to manifest functional decline during the second year of life. Moreover, most patients in our cohort belong to the public health system, but even the two patients from the private system had difficulties obtaining drug therapy at the appropriate dosages.

Adherence to cysteamine therapy is a major problem associated with less favorable outcomes. Intra-leukocyte cystine quantification to monitor compliance and control dosage is not routinely performed in Chile; it requires fresh blood samples that must arrive in less than 24 hours at external laboratories overseas.

The genetic analysis yielded a 100% mutation detection rate, resulting 5 out of the 7 cases homozygous del57kb carriers according to LDM/D17S829 PCR results, which emerges as a cost-effective diagnostic method in comparison to measuring intra-leukocyte cystine. Case P7 was the first Chilean case genetically tested in 2017 and harbored the del57kb mutation in homozygosis [20]. The del57kb mutation involves a major portion of the *CTNS* gene that originated in Germany and is frequently detected in Europe. The Chilean population is recognized as an admixed population secondary to the migration of Europeans since the XV century [21].

Additionally, rare recessive diseases are associated with endogamy, and all our patients were homozygous carriers. A study involving genetic and demographic patterns was performed in Chile, showing that most consanguineous marriages occurred among first cousins, but none of the parents of our patients recognized consanguinity before second-degree relatives [22].

We identified a novel allele in exon 12 that cannot be ruled out as a variant of European origin. However, it might also have arisen in Native Amerindians or even Asians before settlement in America. In terms of the certainty of the diagnosis in this patient, NIC was confirmed by quantifying intra-leukocyte cystine. The single NJC patient carried a variant in exon 7 described as a variant of Spanish origin, compatible with the European ancestry in the Chilean population [23].

We confirmed a heterozygous carrier status in all the families that requested parent testing, which will facilitate access to genetic counseling for forthcoming gestations. They may also be considered for living donor studies in the future.

Analyses of *CTNS* variants in other Latin American countries, particularly Mexico and Brazil, have shown that one-third of all cystinosis diagnosed patients carry the del57kb variant [24–25]. Although our dataset is limited and patient recruitment might be

biased, based on our results, we propose to assay the presence of del57kb firstly and, if negative, sequence all *CTNS* exons in suspected patients with recognized European ancestry.

The impact of different genetic variants as determinants of clinical evolution has not shown a difference between types of *CTNS* mutations and kidney survival [8, 26, 27]. In our cohort, the truncating del57kb variant was exclusively found in the infantile form of cystinosis, suggesting it might be associated with the early development of the disease symptoms. Carriers of *CTNS* truncating mutations with late CKD stage 5 have been reported worldwide, highlighting opportune diagnosis and precocious cysteamine therapy as key factors for improving kidney survival [26, 27].

A promising therapeutic approach has been developed in cystinosis mouse models and culminated with the approval of a Phase 1/2 clinical trial in cystinosis patients. Briefly, the authors will perform autologous transplantation of CD34 hematopoietic stem and progenitor cells modified *ex vivo* using a GMP lentiviral vector to introduce the cystinosin protein (product name: CTNS-RD-04). The impact on clinical outcomes and cystine levels will be evaluated over two years [28].

Conclusions

Developing countries face many challenges and disparities in providing NIC/NJC patients with adequate healthcare. Opportune genetic testing may facilitate early diagnosis and treatment known to be associated with better outcomes. Financed evidence-based standardized protocols are required to generate public policies with multidisciplinary approaches to benefit patients with rare diseases such as nephropathic cystinosis.

Declarations

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Figures

Figure 1

Legend not included with this version.

Figure 2

Legend not included with this version.

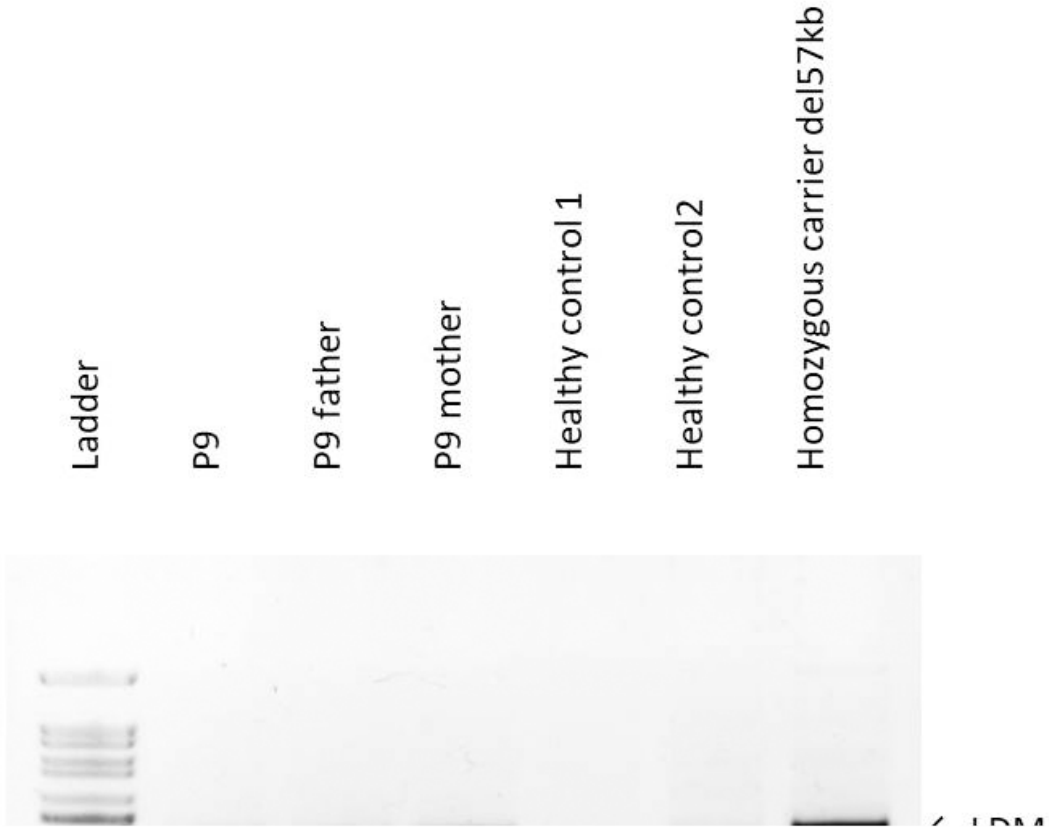

Figure 3

Legend not included with this version.

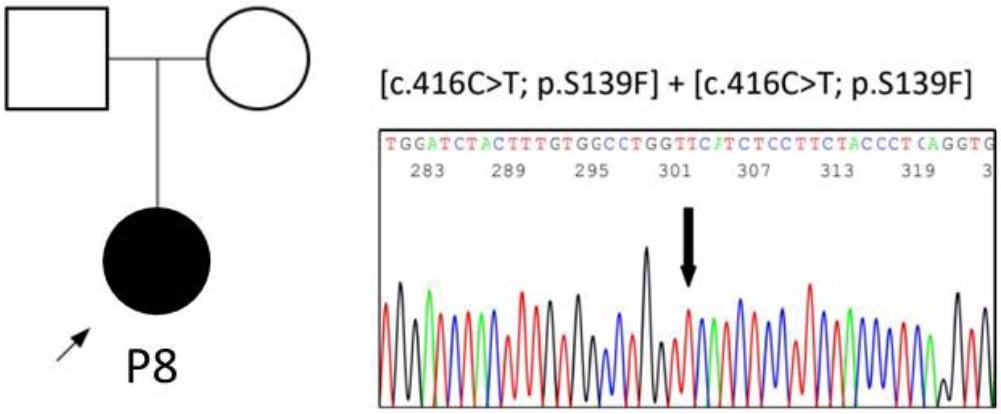

Figure 4

Legend not included with this version.