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Chronic Kidney Disease in Propionic Acidemia

Oleg A. Shchelochkov, MD[1], **Irini Manoli, MD, PhD**[1], **Jennifer L. Sloan, PhD, MS**[1], **Susan Ferry, BSN**[1], **Alexandra Pass, BA**[1], **Carol Van Ryzin, MS**[1], **Jennifer Myles, MS**[2], **Megan Schoenfeld, BS**[2], **Peter McGuire, MS, MD**[1], **Douglas R. Rosing, MD**[3], **Mark D. Levin, MD**[3], **Jeffrey B. Kopp, MD**[4], **Charles P. Venditti, MD, PhD**[1,*]

[1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD.

[2]Nutrition Department, Clinical Research Center, National Institutes of Health, Bethesda, MD.

[3]National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD.

[4]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD.

Abstract

Purpose—Propionic acidemia (PA) is a severe metabolic disorder characterized by multiorgan pathology, including renal disease. The prevalence of chronic kidney disease (CKD) in PA patients and factors associated with CKD in PA are not known.

Methods—Thirty-one subjects diagnosed with PA underwent laboratory and clinical evaluations through a dedicated natural history study at the NIH (ClinicalTrials.gov identifier: NCT02890342).

Results—Cross-sectional analysis of the creatinine-based estimated glomerular filtration rate (eGFR) in subjects with native kidneys revealed an age-dependent decline in renal function ($P < 0.002$). Among adults with PA, 4/8 (50%) had eGFR <60 mL/min/1.73 m^2. There was a significant discrepancy between eGFRs calculated using estimating equations based on serum creatinine compared to serum cystatin C ($P < 0.0001$). The tubular injury marker, plasma lipocalin-2, and plasma uric acid were strongly associated with CKD ($P < 0.0001$). The measured 24-hour creatinine excretion was below normal, even after adjusting for age, height, and sex.

Conclusions—CKD is common in adults with PA and is associated with age. The poor predictive performance of standard eGFR estimating equations, likely due to reduced creatine synthesis in kidney and liver, could delay the recognition of CKD and management of ensuing complications in this population.

*Corresponding author: Charles P. Venditti, Building 10, Room 7N248A, National Institutes of Health, Bethesda, MD 20892-4472, Office phone: 301-496-6213, FAX: 301-402-4929, venditti@mail.nih.gov.

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Keywords

propionic acidemia; chronic kidney disease; GFR; cystatin C; creatinine

Introduction

Propionic acidemia (PA) is a metabolic disorder that carries a marked risk for multiorgan pathology[1]. Chronic kidney disease (CKD, here narrowly defined as the glomerular filtration rate <60 ml/min/1.73 m^2) has been recognized with increased frequency as a complication in patients with organic acidemias, especially methylmalonic acidemia (MMA), and more recently, in other categorically related disorders such as PA and glutaric aciduria type I.[2–7] In PA, the prevalence, natural history, and factors associated with CKD are incompletely defined.

Studies focused on renal function in PA are scant. An association between PA and CKD was first suggested in 1997 by Lehnert et al.[6] Subsequent PA patient case reports of renal failure in a 45-year old woman with CKD [5] and another who presented with stage 3 CKD in the third decade of life[7] have been bolstered by registry observations suggesting that the risk of developing CKD in PA increases with age.[2] In addition, a recent retrospective case review study of liver transplantation in PA showed that half of patients (4/8) were in stage 2 CKD before the procedure, and 100% of patients (4/4) were in stage 2–3 CKD in the post-transplant period.[8] In yet another European series, 2/6 patients developed kidney dysfunction after receiving a liver transplant when their diet was liberalized.[9] These clinical observations suggest that CKD is an under-recognized disease-related complication in PA, especially in adults.

Due to the ramifications of a CKD diagnosis for routine monitoring and long-term management, it is important to define the natural history of renal involvement in PA especially because traditional markers of kidney disease, such as increases in blood urea and serum creatinine, may be obscured by the ingestion of a low protein diet and decreased muscle mass, both of which are common in the PA patient population. We have therefore studied a large and genetically heterogenous cohort of PA patients enrolled in a natural history protocol to approximate the incidence of CKD and identify risk factors associated with progression. Our observations provide important new insights into the manifestations of CKD in PA patients and help establish a framework for the prospective monitoring and the laboratory assessment of renal complications in this population.

Materials and Methods

Patient cohort and protocols

The diagnosis of PA was confirmed using a combination of biochemical, clinical and molecular testing before consent and enrollment into a natural history study (ClinicalTrials.gov Identifiers: NCT02890342). Study protocol was reviewed and approved by the NIH IRB. All subjects or their legal guardians provided written informed consent. Thirty-one individuals with PA, ages 4–53 years, were evaluated over the course of a week-

long admission at the NIH Clinical Research Center. Four individuals were of the African American descent (4/31, 13%), 23/31 (74%) were Caucasian, and 4/31 (13%) were Hispanic. Clinical data were further enriched using selected results, such as genotype, obtained from outside clinical records, or values from other NIH protocols (ClinicalTrials.gov Identifiers: NCT00369421 and NCT01780168) when subjects were co-enrolled.

Clinical and laboratory studies

Testing related to renal function included the measurements of blood pressure, serum creatinine, cystatin C, plasma bicarbonate, total serum calcium, phosphorus, 25-OH-vitamin D, 1,25-OH-vitamin D, intact parathyroid hormone (PTH), erythropoietin, and 24-hour creatinine clearance. Imaging included abdominal ultrasound and transthoracic echocardiography. In pediatric patients (ages <19 years), eGFR was calculated using the updated creatinine-based Schwartz bedside equation (2009)[10] and cystatin C-based Schwartz equation (2012).[11] In patients >19 years of age, eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation (2009),[12] and the CKD-EPI Cystatin C Equation (2012).[13]

Statistics

Creatinine-based, and cystatin C-based methods of estimating GFR were compared either using a paired t-test of the means after checking normality with the D'Agostino-Pearson test or using linear regression fitting followed by the slope and intercept comparisons. Kidney growth analysis in pediatric PA patients was performed on the maximal renal length data, using a slope and intercept comparison to a published reference group matched for age and sex [14]. To compare daily creatinine excretion among PA subjects, age-, height-, and sex-adjusted z-scores were calculated using the means and standard deviations from published reference populations.[15,16] A P value <0.05 was interpreted as statistically significant. Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software, La Jolla, CA).

Results

Patient Characteristics

Selected clinical, genetic, and laboratory parameters are summarized in Table 1. Among 31 participants, 55% were female and 26% of the participants were older than 19 years of age. Biallelic pathogenic variants were present in *PCCA* (13 subjects) and *PCCB* (17 subjects) (Table 1). In one participant, molecular confirmation was not obtained. Three participants (3/31, 10%) had received a liver transplant for metabolic instability - at ages 9, 13, and 35 months.

Renal Indices

The mean renal length in PA subjects, irrespective of the underlying renal function estimates, was similar to the published control populations (Supplemental Figures 1A and 1B). Three patients (10%) had simple renal cysts (Supplemental Figure 2). In this cross-sectional cohort, the frequency of simple cysts was comparable to the prevalence of simple

renal cysts in the general population (10.7% in Chang et al).[17] Low serum phosphate was identified in 1/31 (3%), low 1,25-OH-vitamin D was present in 2/31 (6%), elevated intact PTH was present 3/31 (10%), elevated total serum calcium was present in 3/31 (10%), low plasma bicarbonate was present in 10/31 (32%), and a history of hypertension was present in 6/31 (19%) (Table 1). Nine of 31 participants were taking β-blockers for cardiac indications and one participant was also taking an angiotensin II receptor blocker for hypertension, which affected our ability to assess whether hypertension was present at the time of evaluation. Transthoracic echocardiogram revealed reduced left ventricular contractility in 4/31 patients (13%). Erythropoietin was elevated in 7/27 subjects (26%) and correlated with bone marrow suppression. Cross-sectional analysis of creatinine eGFR in non-transplanted patients suggested an age-dependent pattern of renal function decline (Figure 1A, P value <0.002, $r = -0.536$). However, the cystatin C eGFR in non-transplanted patients revealed that eGFR was reduced in in the first decade of life and progressively declined in some subjects in adulthood (Figure 1B). In pediatric patients, creatinine and cystatin C eGFRs showed significant discrepancy (Figure 1C, P value <0.0001). In adults, the prevalence of an eGFR <60 mL/min/1.73 m^2 was 50% (4/8) by both the CKD-EPI creatinine-based (2009) formula and the CKD-EPI cystatin C equation (2012) (Figure 1C). However, across all ages and all CKD categories (stages G2-G4), creatinine eGFRs classified only 4/31 (13%) patients as having CKD, while the cystatin C eGFRs classified 25/30 patients (82%) to have an eGFR <90 mL/min/1.73 m^2 (Fisher's exact test, P value <0.0001). When we compared regression lines of the creatinine eGFR and cystatin C eGFR in non-transplanted patients (Figure 1D), the Y-axis intercept of the creatinine eGFR regression line was significantly higher than the intercept for cystatin C eGFR (P value < 0.0001) and the difference between slopes approached statistical significance (P value = 0.0508).

We reasoned that sources of discrepancy between the creatinine and cystatin C eGFR in PA patients could be due to lower-than-average serum creatinine concentrations resulting from either impaired growth, sarcopenia, meat-restricted diets, reduced methionine intake, diminished synthesis of creatine in the liver, and/or increased tubular secretion of creatinine. Therefore, to explore potential relationships between these variables, we performed linear regression analyses between serum creatinine or cystatin C, using protein consumption, intake of protein equivalent from medical foods, height, body mass index, and body composition measured by whole-body DEXA as independent variables (Supplemental Table 1).

Surprisingly, we found no association between serum creatinine and % lean body mass or dietary composition and next evaluated daily creatinine excretion adjusted for age, height, and sex.[15,16] The average adjusted z-scores for 24-hour creatinine excretion were −0.536 in PA girls (n=6) and −0.513 in PA boys (n=5) (Supplemental Table 2). One adult male patient had a daily creatinine excretion z-score of −2.518. In adult female patients, the daily average adjusted z-score of creatinine excretion was −1.622 (n=5). The finding that PA patients have a below-average creatinine excretion was corroborated by the high prevalence of elevated urinary protein/creatinine ratio (13/21 patients, 62%). However, only 3 of 18 (17%) patients showed minimal proteinuria on 24-hour urine protein analyses, and the rest had normal protein excretion (Supplemental Figure 3). Lastly, we performed an unbiased linear regression analysis between creatinine or cystatin C and other clinical and laboratory

parameters, which revealed associations with parameters implicated in mechanisms of renal dysfunction including serum uric acid, prealbumin, measured plasma osmolality, plasma lipocalin 2, intact parathyroid hormone, total serum calcium, and left ventricular ejection fraction (Supplemental Table 1).

Discussion

The improved ascertainment and survival of patients with PA over the last several decades mandates recognition of long-term complications. Although recent publications have suggested an association of CKD with propionic acidemia,[2,5,7] the prevalence of CKD has remained difficult to establish since reported data derive mainly from either isolated case reports, small patient series, and registries. Therefore, we sought to investigate renal disease in a study populated with a relatively large, clinically diverse, and genetically heterogeneous cohort of PA patients that included ~25% adults.

Using the accepted definition of eGFR <60 mL/min/1.73 m^2, we observed an unexpectedly high prevalence of CKD (50%) among adult PA patients. While this value is lower than the nearly universal prevalence of CKD seen in *mut*^{0} methylmalonic acidemia patients,[4] it is higher than what has been reported (~15%) in adult PA patients in the E-IMD registry.[2] After extending our analyses to younger patients, we identified a significant discrepancy between creatinine and cystatin C GFRs, with the bedside Schwartz creatinine-based equation (2009) resulting in significantly higher GFR estimates compared to those generated using the cystatin C-based equation. We hypothesized that higher creatinine GFR estimates could be the result of lower serum creatinine levels driven by sarcopenia, diet, or impaired creatine synthesis in the liver. While we did not observe an association between the percent lean body weight and serum creatinine, we found that PA patients had low adjusted daily creatinine excretion. Therefore, we suggest that PA can lead to the reduction of whole-body creatine synthesis, which is likely the result of a combination of dietary and metabolic influences. Several factors inherent to organic acidemias, but known to affect whole-body creatine synthesis, could lead to lower plasma creatinine, and thus bias GFR estimates. These could include dietary restriction of methionine and branched-chain amino acids, reduced intake of meats, low levels of physical activity, and/or impaired energy metabolism in the liver and muscle arising from the mitochondrial dysfunction.[18]

The cellular mechanisms underlying the decline in renal function in propionic acidemia have not been elucidated. While the evaluation of blood and urinary parameters in our study did not reveal a specific pattern that would point to a dominant mechanism(s) of injury (Supplemental Table 1 and Supplemental Figure 3), our observations are consistent with a single published case report describing non-specific tubulointerstitial pathology and glomerular sclerosis.[7] Likewise, the associations between serum creatinine or cystatin C and plasma lipocalin-2, similar to MMA,[19] further suggest the role of ongoing tubular injury in the etiology of CKD in PA.

Without direct GFR measurements, this study cannot resolve the question whether cystatin C eGFR is superior to creatinine eGFR to establish the diagnosis of CKD. Although we did not measure eGFR using iothalamate or iohexol clearance, which, unlike creatinine, are not

affected by renal tubular secretion, the constellation of laboratory and imaging studies featured in this paper clearly establish renal insufficiency in many patients. The cross-sectional study design further limits our ability to establish the progression of the renal disease, and a participation bias may exist. Detailed protocol-based evaluations of all patients, irrespective of the clinical suspicion of any organ system involvement, enabled observations of renal complications and associated laboratory parameters. In particular, measurements of cystatin C, plasma uric acid, 25-OH-vitamin D, 1,25-OH-vitamin D, PTH, plasma osmolality, and 24-hour protein excretion in PA subjects suggest their usefulness as part of CKD surveillance.

The late recognition of kidney disease in PA can impede the initiation of renal protective therapies aimed at delaying the onset or slowing the progression of CKD, such as aggressive control of the acid/base status, control of blood pressure through inhibition of renin-angiotensin system, and urate-lowering therapy.[20] The diagnosis of CKD might also inform decisions about the optimal timing for liver or combined organ transplantation. Since PA patients have minimal hepatic capacity to metabolize propionic acid, renal excretion is needed to clear “toxic” metabolites, which, by virtue of increased concentrations in the setting of renal insufficiency, might contribute to disease progression in other organ systems. For example, whether worsening kidney disease has cardiac consequences seems possible, given that we observed a strong negative correlation between the left ventricular ejection fraction and renal indices in PA patients with CKD categories G3 and G4.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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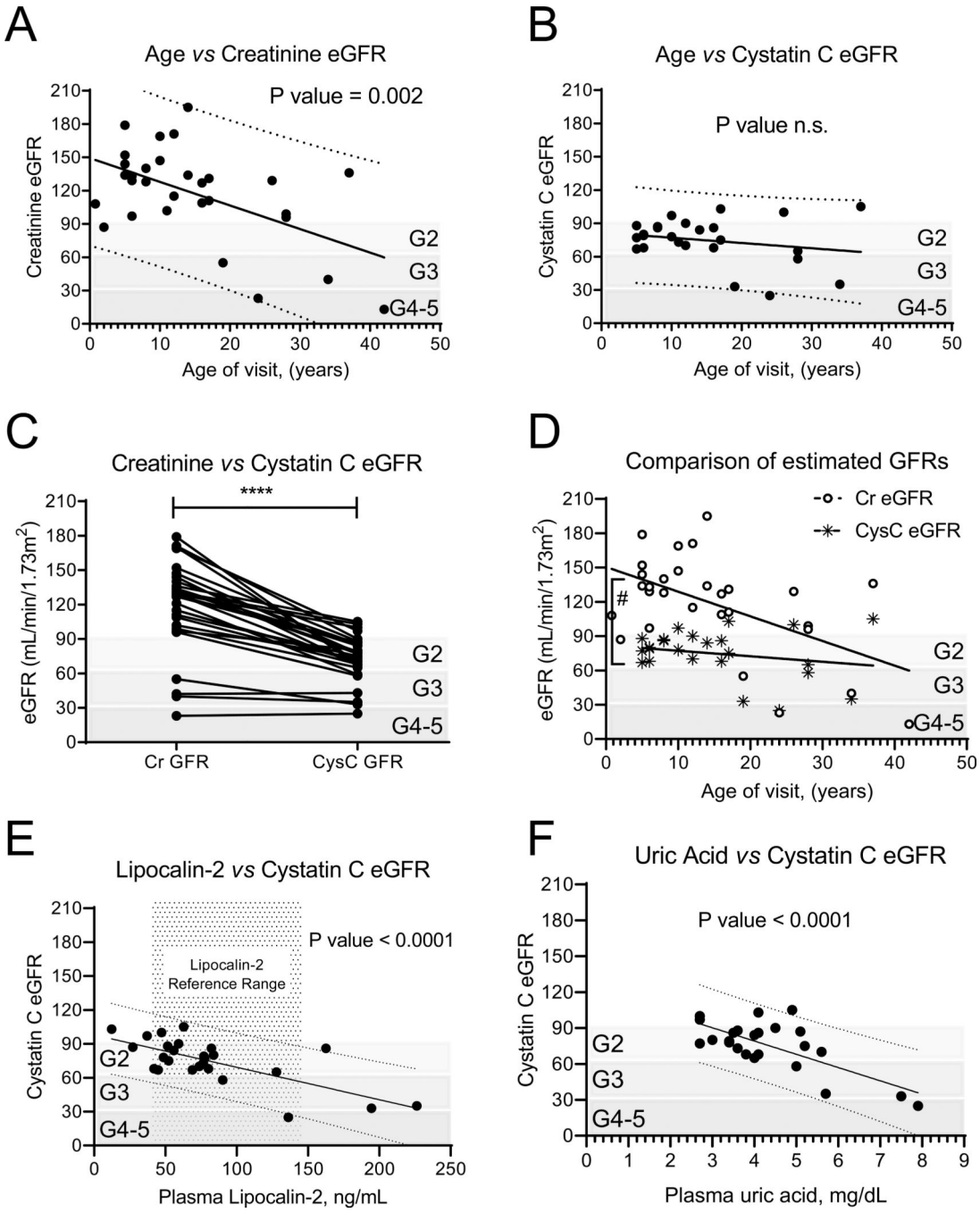

Figure 1. Significant discrepancy between the creatinine and cystatin C GFR estimates and select laboratory parameters associated with declining eGFR.

A. Cross-sectional analysis of creatinine eGFR in non-transplanted patients suggested an age-dependent trend of renal function decline (P value <0.002, $r = -0.536$). G2, G3 and G4–5 denotes levels of renal function based on eGFR. **B.** Cystatin C eGFR in non-transplanted patients suggested the eGFR was reduced in early childhood, with progressive decline in some subjects in the late teen-age or early adult years; 25/30 subjects (82%) had eGFR <90 mL/min/1.73 m^2 (chronic kidney disease stages 2–4). **C.** Creatinine (Cr eGFR) and cystatin

C eGFRs (CysC eGFR) showed significant disagreement (P value <0.0001). **D.** Linear regression of creatinine eGFR and cystatin C eGFR in non-transplanted patients demonstrated that the intercept of the creatinine eGFR was significantly different from cystatin C eGFR (P value < 0.0001, denoted by the # sign). **E**. Plasma lipocalin-2, a biomarker of tubular injury, was associated with the cystatin C eGFR (P value <0.0001, $r = -0.717$). **F**. Plasma uric acid, a factor that can be associated with CKD, rises with decreasing cystatin C eGFR (P value <0.0001, $r = -0.718$). Dotted lines in **Figures 1A, 1B, 1E,** and **1F** represent 95% prediction bands.

Table 1.

Demographics, Genetics, and Renal-Related Findings in the NIH Propionic Acidemia Cohort.

Age of Visit, (years)	Gene	Transplant Status	Variant 1 (cDNA)	Variant 1 (protein)	Variant 2 (cDNA)	Variant 2 (protein)	Crt eGFR	CysC eGFR	Renal-Related Manifestations
4	*PCCA*	LT	c.1288C>T	p.Arg430Ter	c.776T>G	p.Leu259Arg	142	67	↑EPO
6	*PCCA*	NT	c. 1284+1G>A	Canonical Splice	c.1684T>C	p.Ser562Pro	133	79	
6	*PCCA*	LT	c.782A>G	p.Glu261Gly	c.923dupT	p.Leu308Phefs*35	121	59	↓HCO_3
8	*PCCA*	NT	c. 1284+1G>A	Canonical Splice	c.1684T>C	p.Ser562Pro	140	86	
10	*PCCA*	NT	c.742G>A	p.Glu248Lys	c.1430G>T	p.Val478_Gly514del[1]	147	78	HT, ↓HCO_3
10	*PCCA*	NT	c.802C>T	p.Arg268Cys	c.1899+4_1899+7delAGTA	p. p.Cys616_Val633del[2]	169	97	
11	*PCCA*	NT	Deletion of exons 23 and 24	n.a.	Deletion of exons 23 and 24	n.a.	102	73	↓vitD, ↑EPO
12	*PCCA*	NT	c.893A>G	p.Lys298Arg	Deletion of exons 13–20	n.a.	115	70	
12	*PCCA*	NT	c.1284+1G>A	Canonical Splice	c.2027del	p.Lys676Serfs*6	171	90	↑EPO, ↓HCO_3
14	*PCCA*	NT	c.722delG	p.Gly241Valfs*19	c.722delG	p.Gly241Valfs*19	195	n.a.	
16	*PCCA*	NT	c.1268C>T	p.Pro423Leu	c.1899+4_1899+7delAGTA	p. p.Cys616_Val633del[2]	127	86	
34	*PCCA*	NT	c.600+1G>A	Canonical Splice	c.2119–9A>G	Intronic	40	35	↑PTH, ↓HCO_3, ↓LVEF
37	*PCCA*	NT	c.1572_1573delGT	p.Gln524Hisfs*29	c.434T>C	p.Phe145Ser	136	105	↓HCO_3
5	*PCCB*	NT	c.683C>T	p.Pro228Leu	c.1218_1231del14ins12	p.Gly407Argfs*14	152	88	↓HCO_3
5	*PCCB*	NT	c.764–2delA	Canonical Splice	c.975_977delTGA	p.Asp325del	179	67	
5	*PCCB*	NT	c.386_387delTTinsAAC	p.Phe129Ter	c.1606A>G	p.Asn536Asp	134	77	↑Phos, ↓HCO_3
5	*PCCB*	NT	c.764–2delA	Canonical Splice	c.975_977delTGA	p.Asp325del	144	67	HT
6	*PCCB*	NT	c.683C>T	p.Pro228Leu	c.1218_1231del14ins12	p.Gly407ArgfsX14	129	68	
6	*PCCB*	LT	c.1259_1260insT	p.Glu421Ter	c.1259_1260insT	p.Glu421Ter	115	71	HT, ↓HCO_3
8	*PCCB*	NT	c.337C>T	p.Arg113Ter	c.1275_1227delATC	p.Ile409del	128	87	↑EPO
14	*PCCB*	NT	c.386_387delTTinsAAC	p.Phe129Ter	c.1552delG	p.Asp518Thrfs*33	134	84	↓HCO_3
16	*PCCB*	NT	c.1172_1173delTT	p.Phe391Cysfs*2	c.1172_1173delTT	p.Phe391Cysfs*2	109	68	
17	*PCCB*	NT	c.1218_1231del14ins12	p.Gly407Argfs*14	c.1218_1231del14ins12	p.Gly407Argfs*14	111	75	↑EPO
17	*PCCB*	NT	c.1218_1231del14ins12	p.Gly407Argfs*14	c.990dupT	p.Glu331Ter	131	103	HT, ↑EPO
19	*PCCB*	NT	c.1204delG	p.Ala402Hisfs*41	c.335G>A	p.Gly112Asp	55	33	HT, ↓vitD, ↑Ca
24	*PCCB*	NT	TBD	TBD	TBD	TBD	23	25	↑PTH, ↑Ca, ↓HCO_3, ↓LVEF
26	*PCCA*	NT	c.716+5G>C	Intronic	c.782A>G	p.Glu261Gly	129	100	↓LVEF
28	*PCCB*	NT	c.734G>A	p.Gly245Asp	Deletion of exon 9	n.a.	99	65	
28	*PCCB*	NT	c.1218_1231del14ins12	p.Gly407Argfs*14	c.1495C>T	p.Arg499Ter	96	58	
53	*PCCB*	KT	c.1142dupG	p.Cys381Trpfs*2	c.1606A>G	p.Asn536Asp	55	53	HT, ↑PTH, ↑Ca, ↑EPO

Age of Visit, (years)	Gene	Transplant Status	Variant 1 (cDNA)	Variant 1 (protein)	Variant 2 (cDNA)	Variant 2 (protein)	Crt eGFR	CysC eGFR	Renal-Related Manifestations
6	TBD	NT	TBD	TBD	TBD	TBD	97	80	↓LVEF

Abbreviations (in the alphabetical order): ↑Ca – elevated high total serum Ca; cDNA – coding DNA; Crt eGFR – creatinine eGFR expressed in mL/min/1.73 m^2; CysC eGFR – cystatin C eGFR expressed in mL/min/1.73 m^2; ↑EPO – elevated plasma erythropoietin; ↓HCO_3 – low plasma bicarbonate; HT – hypertension; KT – kidney transplant; LT – liver transplant; ↓LVEF – low left ventricular ejection fraction; n.a. – not available; NT – not-transplanted; ↑Phos – elevated serum phosphorus; ↑PTH – elevated intact parathyroid hormone; TBD – to be determined; ↓vitD – low 1,25-OH-vitamin D.

[1]This variant most likely results in exon 17 skipping.

[2]This variant most likely results in exon 21 skipping.