SUPPLEMENTAL MATERIAL

Phenotype-Genotype Correlations and Estimated Carrier Frequencies of Primary Hyperoxaluria

Katharina Hopp[1+], Andrea G Cogal[1+], Eric J Bergstralh[2], Barbara M Seide[1], Julie B Olson[1], Alicia M Meek[1], John C Lieske[1], Dawn S Milliner[1, 4], Peter C Harris[1,3*], on behalf of the Rare Kidney Stone Consortium

[+]These authors contributed equally to this work

[1]Division of Nephrology and Hypertension, [2]Division of Biomedical Statistics and Informatics, [3]Department of Biochemistry and Molecular Biology, [4]Division of Pediatric Nephrology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Corresponding Author:

[*]Peter C. Harris

Division of Nephrology and Hypertension

Mayo Clinic

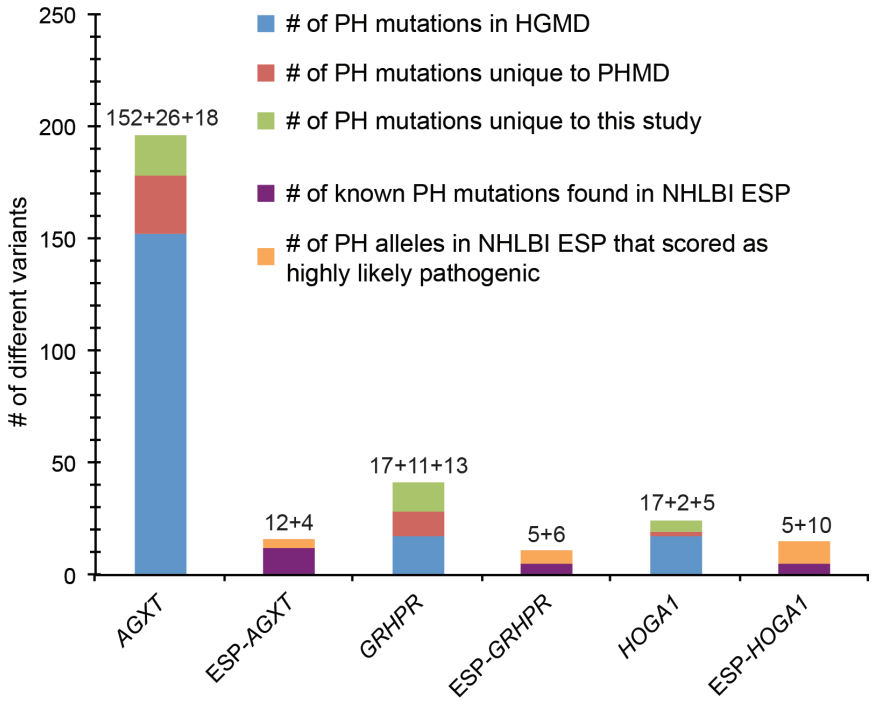
200 First Street SW

Rochester, MN 55905

Phone: 507-266-0541

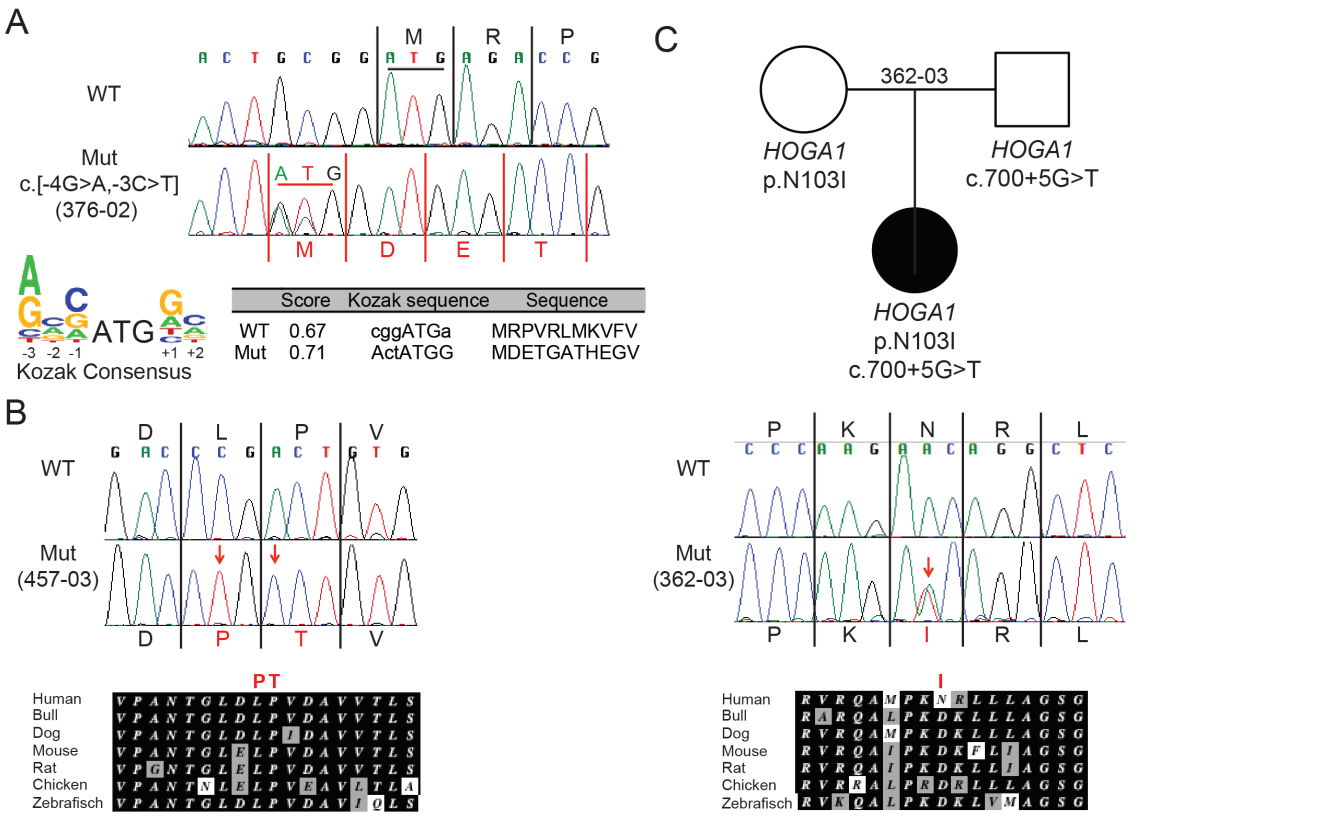
Fax: 507-266-9315

email: harris.peter@mayo.edu

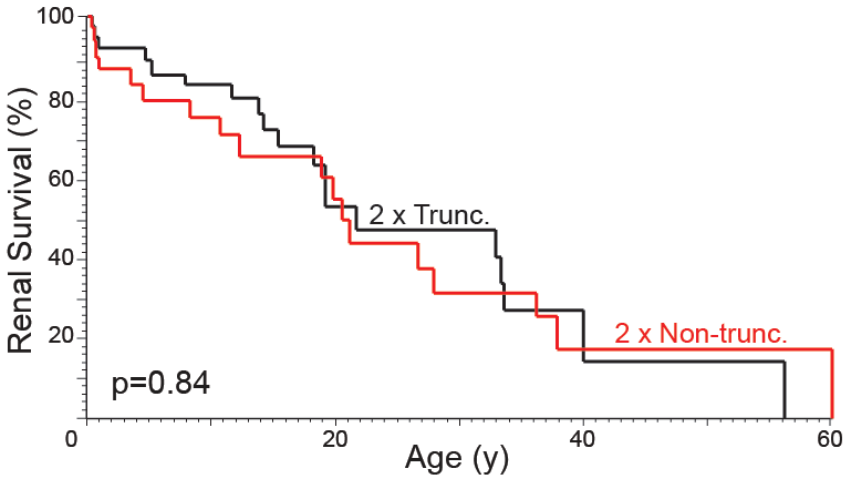


Supplemental Figure 1 | Number summary of different PH alleles in mutation databases and the NHLBI ESP.

Graph depicting the number of PH mutant alleles identified to date. Numbers are broken down by mutant alleles recorded in HGMD (blue), additional alleles recorded just in PHMD[1] (red), and novel alleles identified in this study (green, RKSC PH registry, Table 1). ESP: Number of PH mutations found within the NHLBI whole exome sequencing data set[2] (purple, Supplemental Table 7) and number of additional rare variants that scored as highly likely pathogenic within this dataset (orange, Supplemental Table 8).



Supplemental Figure 2 | Depiction of three atypical, novel mutations found within the RKSC PH registry. (A) Sanger chromatogram and *in silico* analysis of the newly identified *GRHPR* transcription start site mutation. As illustrated by the human Kozak consensus sequence and in the table, the double mutation creates a novel and stronger start site at the -4 ATG position, creating a frameshifted novel protein. (B) Sanger chromatogram and multiple sequence alignment (MSA) of the two amino acid substitutions found in the first described PH3 patient to reach ESRD. (C) Pedigree, Sanger chromatogram, and MSA of a novel PH3 variant. This amino acid substitution did not score as highly likely pathogenic in all *in silico* tools (Table 1) because of the substitution found in other orthologs. However, the change in orthologs from asparagine to aspartic acid is chemically conservative while the mutation to a hydrophobic isoleucine is non-conservative.



2 x Trunc.	52% (8)	13% (1)	-
2 x Non-Trunc.	54% (10)	16% (2)	-

Supplemental Figure 3 | Renal survival plot of allelic effect between patients with two *AGXT* non-MiR non-truncating changes versus two *AGXT* truncating changes.
Kaplan-Meier renal survival plot plus survival estimate tables for PH1 patients having either two truncating changes (37 patients) or two non-miR non-truncating changes (30 patients). The comparison shows no significant difference in renal survival between the groups.

Supplemental Table 1 | Evaluation of *AGXT* allelic effects on PH1 severity

	2 x Trunc N=37	2 x Non-trunc N=30	2 x MiR N=69	Trunc + Non-trunc N=14	Trunc + MiR N=60	Non-trunc + MiR N=37	p-value adjusted
Age at Symptoms yrs (median) (Q1, Q3) (Min, Max)	4.3 (0.7, 7.6) (0.2, 37.2) N=33	5.9 (1.0, 9.6) (0.1, 41.5) N=23	10.6 (2.4, 22.0) (0.5, 49.8) N=59	3.6 (1.3, 5.9) (0.2, 11.3) N=12	4.5 (1.6, 10.0) (0.1, 53.0) N=53	7.5 (2.1, 17.0) (0.1, 52.6) N=33	0.028
Nephrocalcinosis yes: N (%) no: N (%)	 11 (42.3%) 15 (57.7%)	 7 (36.8%) 12 (63.2%)	 7 (18.4%) 31 (81.6%)	 3 (37.5%) 5 (62.5%)	 15 (32.6%) 25 (67.4%)	 6 (26.1%) 17 (73.9%)	0.36
Urine Chemistry (median) (Q1, Q3)							
Ox24 mmol/1.73m² (normal < 0.46)*	2.3 (1.6, 2.7) N=12	2.0 (1.7, 3.0) N=13	1.1 (0.7, 1.5) N=26	2.7 (1.8, 4.1) N=7	2.2 (1.5, 2.7) N=42	1.7 (1.3, 2.1) N=21	0.0002
Ca24 mg/1.73m² (normal 100-300)*	49.1 (32.7, 71.1) N=9	58.9 (54.9, 68.3) N=9	79.5 (29.0, 157.5) N=19	34.8 (14.3, 45.5) N=3	57.3 (32.6, 76.6) N=33	51.1 (39.2, 96.2) N=9	0.34
Cit24 mg/1.73m² (normal 320-1240)*	378.6 (67.3, 477.8) N=10	157.7 (79.2, 460.2) N=8	402.5 (125.4, 584.7) N=16	195.1 (105.2, 281.7) N=4	278.4 (158.1, 362.5) N=27	96.1 (78.2, 1073.6) N=9	0.83
Glycolate mg/g creatinine (normal 0-78)**	301.0 (171.0, 458.0) N=9	112.0 (87.5, 267.0) N=12	45.0 (19.0, 143.0) N=23	194.0 (165.0, 276.0) N=5	88.0 (39.5, 186.5) N=32	101.0 (64.0, 182.0) N=15	0.011

*Normal values are for adult patients. Values in table have been adjusted to BSA to permit comparison of adult and pediatric age patients[3, 4].
**Normal values may be higher in children from birth to 5 years of age.
Trunc: nonsense, splice, frameshifting InDel; Non-trunc: missense and inframe InDel; MiR: p.G41R, p.F152I, p.G170R, p.I244T

Supplemental Table 2 | PH1 allelic effects, excluding patients with MiR alleles

	2 x Trunc N=37	Trunc + Non-trunc N=14	2 x Non-trunc N=30	p-value adjusted
Age at Symptoms yrs (median) (Q1, Q3) (Min, Max)	4.3 (0.7, 7.6) (0.2, 37.2) N=33	3.6 (1.3, 5.9) (0.2, 11.3) N=12	5.9 (1.0, 9.6) (0.1, 41.5) N=23	0.63
Nephrocalcinosis yes: N (%) no: N (%)	11 (42.3%) 15 (57.7%)	3 (37.5%) 5 (62.5%)	7 (36.8%) 12 (63.2%)	0.93
Urine Chemistry (median) (Q1, Q3)				
Ox24 mmol/1.73m² (normal < 0.46)*	2.3 (1.6, 2.7) N=12	2.7 (1.8, 4.1) N=7	2.0 (1.7, 3.0) N=13	0.42
Ca24 mg/1.73m² (normal 100-300)*	49.1 (32.7, 71.1) N=9	34.8 (14.3, 45.5) N=3	58.9 (54.9, 68.3) N=9	0.37
Cit24 mg/1.73m² (normal 320-1240)*	378.6 (67.3, 477.8) N=10	195.1 (105.2, 281.7) N=4	157.7 (79.2, 460.2) N=8	0.63
Glycolate mg/g creatinine (normal 0-78)**	301.0 (171.0, 458.0) N=9	194.0 (165.0, 276.0) N=5	112.0 (87.5, 267.0) N=12	0.23

*Normal values are for adult patients. Values in table have been adjusted to BSA to permit comparison of adult and pediatric age patients[3, 4].
**Normal values may be higher in children from birth to 5 years of age.

Supplemental Table 3 | Evaluation of *GRHPR* allelic effects on PH2 severity

	2 x Trunc N=21	Trunc + Non-trunc N=7	2 x Non-trunc N=7	p-value adjusted
Age at Symptoms yrs (median) (Q1, Q3) (Min, Max)	9.2 (3.1, 19.8) (0.6, 39.9) N=18	7.4 (1.4, 15.2) (0.8, 42.0) N=7	4.4 (1.4, 11.1) (1.3, 11.4) N=6	0.76
Nephrocalcinosis (yes) (no)	2 (11.1%) 16 (88.9%)	1 (16.7%) 5 (83.3%)	2 (33.3%) 4 (66.7%)	0.58
Urine Chemistry (median) (Q1, Q3)				
Ox24 mmol/1.73m² (normal < 0.46)*	1.7 (1.5, 1.9) N=13	3.4 (0.7, 4.5) N=6	1.2 (1.1, 1.6) N=4	0.46
Ca24 mg/1.73m² (normal 100-300)*	80.0 (61.9, 141.4) N=13	113.8 (77.2, 131.6) N=4	62.7 (30.0, 95.4) N=2	0.71
Cit24 mg/1.73m² (normal 320-1240)*	892.3 (335.5, 1285.0) N=9	485.1 (74.3, 1372.4) N=4	358.4 (245.2, 1285.0) N=2	0.63
L-glycerate mg/g creatinine (normal 0-8)**	870.0 (579.0, 2640.0) N=13	347.0 (207.5, 705.0) N=2	698.5 (271.0, 1126.0) N=2	0.22

*Normal values are for adult patients. Values in table have been adjusted to BSA to permit comparison of adult and pediatric age patients[3, 4].
**Normal values may be higher in children from birth to 5 years of age.

Supplemental Table 4 | Allelic comparison of PH3 focusing on the most prevalent alleles

	Hom c.700+5G>T N=10	Hom p.E315del N=8	Het/Comp. Het[A] N=16	Other[B] N=4	p-value adjusted
Age at Symptoms yrs (median) (Q1, Q3) (Min, Max)	1.9 (0.4, 4.5) (0.3, 8.7) N=8	1.1 (0.6, 29.0) (0.4, 31.0) N=7	4.4 (1.1, 6.3) (0.3, 28.3) N=14	2.8 (1.1, 4.6) (0.8, 5.1) N=4	0.57
Nephrocalcinosis yes: N (%) no: N (%)	0 (0.0%) 10 (100.0%)	0 (0.0%) 8 (100.0%)	1 (6.3%) 15 (93.8%)	0 (0.0%) 3 (100.0%)	0.72
Urine Chemistry (Median) (Q1, Q3)					
Ox24 mmol/1.73m² (normal < 0.46)*	1.0 (0.7, 1.3) N=10	1.0 (0.8, 1.1) N=6	1.4 (1.1, 1.7) N=15	1.0 (1.0, 1.3) N=3	0.17
Ca24 mg/1.73m² (normal 100-300)*	82.1 (53.1, 153.0) N=6	113.7 (82.7, 147.7) N=5	77.3 (57.8, 142.1) N=12	133.6 (72.3, 230.1) N=3	0.43
Cit24 mg/1.73m² (normal 320-1240)*	573.3 (189.6, 698.8) N=6	452.2 (416.3, 780.5) N=5	710.9 (482.8, 915.7) N=13	710.5 (405.7, 1073.7) N=3	0.47

[A]common alleles c.700+5G>T and p.E315del
[B]2 x Non-trunc, Non-trunc + nonsense; note: only one PH3 patient carried a Trunc change heterozygously
*Normal values are for adult patients. Values in table have been adjusted to BSA to permit comparison of adult and pediatric age patients[3, 4].

Supplemental Table 5 | Phenotypic heterogeneity associated (A) with homozygotes for common PH alleles and (B) among NMD patients

A

	# of patients	Age at symptoms (yrs) (min/max)	Nephro-calcinosis (#yes/no)	Ox24 mmol/1.73m^2 (min/max)	eGFR[A] ml/min/1.73m^2 (min(yrs)/max(yrs))	# of patients with ESRD	Age at ESRD (yrs) (min/max)
PH 1							
c.33dupC	13	0.2/37.2	5/6	1.74/2.68	12(1.0)/58(47.9)	9	0.4/55.8
p.G170R	29	0.6/49.8	1/13	0.39/12.5	73(0.0)/68(57.7)	17	0.6/67.6
p.I244T	13	0.5/41.3	4/4	1.12/1.20	47(14.1)/73(41.6)	8	0.2/31.0
PH 2							
c.103delG	10	0.6/39.9	1/7	1.03/2.41	2(21.5)/49(60.1)	1	21.5
PH 3							
c.700+5G>T	10	0.3/8.7	0/10	0.49/1.41	74(3.6)/101(20.3)	0	N/A
p.E315del	8	0.4/31.0	0/8	0.71/2.89	99(0.6)/58(70)	0	N/A

[A]The reported eGFR/Age pairs are lowest eGFR at youngest age and highest eGFR at oldest age

B

	# of patients	Age at symptoms (yrs) (min/max)	Nephro-calcinosis (#yes/no)	Ox24 mmol/1.73m^2 (min/max)	eGFR[A] ml/min/1.73m^2 (min(yrs)/max(yrs))	# of patients with ESRD	Age at ESRD (yrs) (min/max)
NMD	35	0.1/69.7	6/24	0.14/2.68	84(4.0)/59(62.5)	2	62.4/66.9

[A]The reported eGFR/Age pairs are lowest eGFR at youngest age and highest eGFR at oldest age

Supplemental Table 6 | List of PH mutant alleles found in the NHLBI ESP

Gene	GRCh37 position	cDNA	Protein	Source DB[A]	EA Allele Count[B]	AA Allele Count[B]	All Allele Count[B]	EA MAF[C] (%)	AA MAF[C] (%)	All MAF[C] (%)	EA Genotype Count[D]	AA Genotype Count[D]	All Genotype Count[D]	Avr. Sample RD[E]
AGXT	2:241808284	c.2T>C	p.(M1T)	HGMD/PHDB	0/8596	1/4395	1/12991	0	0.023	0.008	CC=0/CT=0/TT=4298	CC=0/CT=1/TT=2197	CC=0/CT=1/TT=6495	22
AGXT	2:241808389	c.107G>A	p.(R36H)	HGMD/PHDB	0/8598	1/4405	1/13003	0	0.023	0.008	AA=0/AG=0/GG=4299	AA=0/AG=1/GG=2202	AA=0/AG=1/GG=6501	46
AGXT	2:241808753	c.332G>A	p.(R111Q)	HGMD/PHDB	1/8599	0/4406	1/13005	0.012	0	0.008	AA=0/AG=1/GG=4299	AA=0/AG=0/GG=2203	AA=0/AG=1/GG=6502	62
AGXT	2:241810796	c.454T>A	p.(F152I)	HGMD/PHDB/RKSC	3/8591	0/4396	3/12987	0.035	0	0.023	AA=0/AT=3/TT=4294	AA=0/AT=0/TT=2198	AA=0/AT=3/TT=6492	26
AGXT	2:241810808	c.466G>A	p.(G156R)	HGMD/PHDB/RKSC	1/8593	0/4396	1/12989	0.012	0	0.008	AA=0/AG=1/GG=4296	AA=0/AG=0/GG=2198	AA=0/AG=1/GG=6494	28
AGXT	2:241810850	c.508G>A	p.(G170R)	HGMD/PHDB/RKSC	10/8578	0/4392	10/12970	0.116	0	0.077	AA=0/AG=10/GG=4284	AA=0/AG=0/GG=2196	AA=0/AG=10/GG=6480	24
AGXT	2:241812395	c.525-1G>A	N/A	HGMD/PHDB/RKSC	1/8599	0/4406	1/13005	0.012	0	0.008	AA=0/AG=1/GG=4299	AA=0/AG=0/GG=2203	AA=0/AG=1/GG=6502	93
AGXT	2:241813402	c.603C>A	p.(D201E)	HGMD/PHDB/RKSC	1/8599	0/4406	1/13005	0.012	0	0.008	AA=0/AC=1/CC=4299	AA=0/AC=0/CC=2203	AA=0/AC=1/CC=6502	106
AGXT	2:241814542	c.697C>T	p.(R233C)	HGMD/PHDB/RKSC	0/8600	2/4404	2/13004	0	0.045	0.015	TT=0/TC=0/CC=4300	TT=0/TC=2/CC=2201	TT=0/TC=2/CC=6501	89
AGXT	2:241815397	c.822G>C	p.(E274D)	HGMD/PHDB	2/8598	0/4406	2/13004	0.023	0	0.015	CC=0/CG=2/GG=4298	CC=0/CG=0/GG=2203	CC=0/CG=2/GG=6501	118
AGXT	2:241816973	c.866G>A	p.(R289H)	PHDB	2/7820	7/4033	9/11853	0.026	0.173	0.076	AA=0/AG=2/GG=3909	AA=0/AG=7/GG=2013	AA=0/AG=9/GG=5922	17
AGXT	2:241817471	c.976delG	p.(V326fs)	HGMD/PHDB/RKSC	1/8247	0/4266	1/12513	0.012	0.000	0.008	DelDel=0/DelRef=1/RefRef=4123	DelDel=0/DelRef=0/RefRef=2133	DelDel=0/DelRef=1/RefRef=6256	37
GRHPR[1]	9:37424858	c.103delG	p.(D35fs)	HGMD/PHDB/RKSC	11/8243	5/4259	16/12502	0.133	0.117	0.128	[4]DelDel=0/DelRef=11/RefRef=4116	[4]DelDel=0/DelRef=5/RefRef=2127	[4]DelDel=0/DelRef=16/RefRef=6243	43
GRHPR	9:37430535	c.626C>T	p.(S209F)	RKSC	0/8600	2/4404	2/13004	0	0.045	0.015	TT=0/TC=0/CC=4300	TT=0/TC=2/CC=2201	TT=0/TC=2/CC=6501	110
GRHPR	9:37430644	c.734+1G>A	NA	RKSC	3/8597	0/4406	3/13003	0.035	0	0.023	AA=0/AG=3/GG=4297	AA=0/AG=0/GG=2203	AA=0/AG=3/GG=6500	61
GRHPR[2]	9:37432037	c.769dupG	p.(A256fs)	RKSC	0/8254	1/4263	1/12517	0	0.024	0.008	InsIns=0/InsRef=0/RefRef=4127	InsIns=0/InsRef=1/RefRef=2131	InsIns=0/InsRef=1/RefRef=6258	146
GRHPR	9:37436696	c.904C>T	p.(R302C)	HGMD/PHDB	1/8599	0/4406	1/13005	0.012	0	0.008	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	204
HOGA1	10:99359537	c.569C>T	p.(P190L)	HGMD/PHDB/RKSC	1/8599	0/4406	1/13005	0.012	0	0.008	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	75
HOGA1	10:99359925	c.700+5G>T	NA	HGMD/PHDB/RKSC	26/8574	2/4404	28/12978	0.302	0.045	0.215	TT=0/TG=26/GG=4274	TT=0/TG=2/GG=2201	TT=0/TG=28/GG=6475	124
HOGA1	10:99371292	c.860G>T	p.(G287V)	HGMD/PHDB/RKSC	1/8599	0/4406	1/13005	0.012	0	0.008	TT=0/TG=1/GG=4299	TT=0/TG=0/GG=2203	TT=0/TG=1/GG=6502	66
HOGA1	10:99371339	c.907C>T	p.(R303C)	HGMD/PHDB/RKSC	1/8599	0/4406	1/13005	0.012	0	0.008	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	45
HOGA1[3]	10:99371368	c.944_946delAGG	p.(E315del)	HGMD/PHDB/RKSC	4/8250	0/4264	4/12514	0.049	0	0.032	DelDel=0/DelRef=4/RefRef=4123	DelDel=0/DelRef=0/RefRef=2132	DelDel=0/DelRef=4/RefRef=6255	39
MTS Allele - AGT Mi[F]														
AGXT	2:241808314	c.32C>T	p.(P11L)		1749/6849	269/4129	2018/10978	20.3419	6.1164	15.5279	TT=186/TC=1377/CC=2736	TT=7/TC=255/CC=1937	TT=193/TC=1632/CC=4673	30
AGXT	2:241817516	c.1020A>G	p.(I340M)		1788/6812	282/4124	2070/10936	20.7907	6.4004	15.9157	GG=191/GA=1406/AA=2703	GG=9/GA=264/AA=1930	GG=200/GA=1670/AA=4633	60

[A] DB: Data Base, HGMD (Professional v27. 2013.3), PHDB (curated by Dr. Gill Rumsby), RKSC (RKSC PH registry)

[B] Represented as Alt/Ref, EA: European American, AA: African American, All: EA+AA

[C] MAF: Minor Allele Frequency

[D] Represented as AltAlt/AltRef/RefRef

[E] RD: Read Depth

[F] The alleles of the *AGXT* "minor allele (AGT-Mi) were not included in the P/CF analysis, MTS: mitochondrial targeting sequence

[1] Recorded in ESP as c.101delG, p.D35fs

[2] Recorded in ESP as c.767_768insG, p.A257fs

[3] Recorded in ESP as c.937_939delGAG, p. E313del

[4] c.103delG was called as DelDel 8 times in ESP6500 (4 in EA, 4 in AA). This likely reflects a miscall due to low coverage of the Alt allele. Hence, these allele and genotype counts were adjusted to reflect DelRef.

Supplemental Table 7 | List of variants found in the NHLBI ESP that scored as highly likely pathogenic using *in silico* tools

Gene	GRCh37 position	cDNA	Protein	Mutation Assesment[A]	EA Allele Count[B]	AA Allele Count[B]	All Allele Count[B]	EA MAF[C] (%)	AA MAF[C] (%)	All MAF[C] (%)	EA Genotype Count[D]	AA Genotype Count[D]	All Genotype Count[D]	Avr. Sample RD[E]
AGXT	2:241808773	c.352C>A	p.(R118S)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	AA=0/AC=1/CC=4299	AA=0/AC=0/CC=2203	AA=0/AC=1/CC=6502	51
AGXT	2:241808774	c.353G>C	p.(R118P)	C65/Affect Protein/Prob Damaging; 7/7	0/8600	1/4405	1/13005	0	0.0227	0.0077	CC=0/CG=0/GG=4300	CC=0/CG=1/GG=2202	CC=0/CG=1/GG=6502	49
AGXT	2:241814555	c.710C>T	p.(P237L)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	92
AGXT	2:241815384	c.809A>G	p.(Y270C)	C55/Affect Protein/Prob Damaging; 5/7[F]	1/8599	0/4406	1/13005	0.0116	0	0.0077	GG=0/GA=1/AA=4299	GG=0/GA=0/AA=2203	GG=0/GA=1/AA=6502	127
GRHPR	9:37426570	c.323C>T	p.(T108I)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	129
GRHPR	9:37426617	c.370C>T	p.(R124C)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	92
GRHPR	9:37429746	c.511C>T	p.(R171C)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	102
GRHPR	9:37430565	c.656C>T	p.(T219I)	C65/Affect Protein/Pos Damaging; 7/7	0/8600	1/4405	1/13005	0	0.0227	0.0077	TT=0/TC=0/CC=4300	TT=0/TC=1/CC=2202	TT=0/TC=1/CC=6502	114
GRHPR[1]	9:37432049	c.780dupT	p.(G261fs)	N/A	0/8254	1/4263	1/12517	0	0.0235	0.0080	InsIns=0/InsRef=0/RefRef=4127	InsIns=0/InsRef=1/RefRef=2131	InsIns=0/InsRef=1/RefRef=6258	150
GRHPR	9:37432076	c.806A>G	p.(D269G)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	GG=0/GA=1/AA=4299	GG=0/GA=0/AA=2203	GG=0/GA=1/AA=6502	152
HOGA1	10:99344660	c.200T>G	p.(F67C)	C65/Affect Protein/Pos Damaging; 4/7[F]	1/8599	0/4406	1/13005	0.0116	0	0.0077	GG=0/GT=1/TT=4299	GG=0/GT=0/TT=2203	GG=0/GT=1/TT=6502	67
HOGA1	10:99358589	c.269T>A	p.(L90H)	C65/Affect Protein/Prob Damaging; 6/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	AA=0/AT=1/TT=4299	AA=0/AT=0/TT=2203	AA=0/AT=1/TT=6502	132
HOGA1	10:99358870	c.365C>T	p.(T122I)	C65/Affect Protein/Pos Damaging; 6/7	2/8598	0/4406	2/13004	0.0233	0	0.0154	TT=0/TC=2/CC=4298	TT=0/TC=0/CC=2203	TT=0/TC=2/CC=6501	93
HOGA1	10:99359453	c.485C>T	p.(P162L)	C65/Affect Protein/Prob Damaging; 6/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	99
HOGA1	10:99359503	c.535C>T	p.(P179S)	C65/Affect Protein/Benign; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2203	TT=0/TC=1/CC=6502	80
HOGA1	10:99359509	c.541G>C	p.(D181H)	C65/Affect Protein/Pos Damaging; 6/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	CC=0/CG=1/GG=4299	CC=0/CG=0/GG=2203	CC=0/CG=1/GG=6502	80
HOGA1	10:99359552	c.584T>C	p.(M195T)	C65/Affect Protein/Benign; 1/7[F]	1/8599	0/4406	1/13005	0.0116	0	0.0077	CC=0/CT=1/TT=4299	CC=0/CT=0/TT=2203	CC=0/CT=1/TT=6502	71
HOGA1	10:99359567	c.599G>A	p.(G200D)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4406	1/13005	0.0116	0	0.0077	AA=0/AG=1/GG=4299	AA=0/AG=0/GG=2203	AA=0/AG=1/GG=6502	61
HOGA1	10:99361698	c.785G>A	p.(W262*)	N/A	0/8600	1/4403	1/13003	0	0.0227	0.0077	AA=0/AG=0/GG=4300	AA=0/AG=1/GG=2201	AA=0/AG=1/GG=6501	30
HOGA1	10:99361724	c.811C>T	p.(R271C)	C65/Affect Protein/Prob Damaging; 7/7	1/8599	0/4402	1/13001	0.0116	0	0.0077	TT=0/TC=1/CC=4299	TT=0/TC=0/CC=2201	TT=0/TC=1/CC=6500	23

[A] *In Silico* scoring, AlignGVGD/SIFT/PolyPhen2; MSA: Multi Sequence Allignment = 7 protein orthologs (human, bull, mouse, rat, dog, chicken, zebrafish)

[B] represented as Alt/Ref, EA: European American, AA: African American, All: EA+AA

[C] MAF: Minor Allele Frequency

[D] represented as AltAlt/AltRef/RefRef

[E] RD: Read Depth

[F] Amino Acids not identical to the reference are either conserved within a chemical group (polar vs. non-polar, hydrophobic, uncharged, acidic, basic) or are in a highly conserved block of amino acids (e.g. novel pathogenic PH3 allele in Suppelmental Figure 2C)

[1] Recorded in ESP as c.779_780insT p.G261fs

Supplemental Table 8 | Carrier frequency and prevalence based on known and predicted PH mutant alleles found in the NHLBI ESP

	European American (EA)	African American (AA)	All (EA+AA)
PH1+PH2+PH3			
Allele Count (Alt/Ref)	87/8,535	25/4,378	112/12,913
Mutant Allele Frequency (%)	1.019	0.571	0.867
Prevalence (1 in)*	25,812	75,481	38,630
Carrier Frequency (1 in)*	49	88	58
PH1 (*AGXT*)			
Allele Count (Alt/Ref)	25/8,526	12/4,371	37/12,897
Mutant Allele Frequency (%)	0.293	0.275	0.287
Prevalence (1 in)	116,308	132,678	121,499
Carrier Frequency (1 in)	171	183	175
PH2 (*GRHPR*)			
Allele Count (Alt/Ref)	19/8,504	10/4,366	29/12,870
Mutant Allele Frequency (%)	0.223	0.229	0.225
Prevalence (1 in)	200,327	190,620	196,952
Carrier Frequency (1 in)	224	219	222
PH3 (*HOGA1*)			
Allele Count (Alt/Ref)	43/8,574	3/4,396	46/12,970
Mutant Allele Frequency (%)	0.502	0.068	0.355
Prevalence (1 in)	39,659	2,147,202	79,499
Carrier Frequency (1 in)	100	733	141

*P was determined by combining the individual prevalence of all PH types with bigenic PH cases counting as carriers.

Supplemental Table 9 | PH and PH1 carrier frequency and prevalence, excluding the common AA allele *AGXT* p.R289H, based on (A) known and (B) known plus predicted PH mutant alleles found in the NHLBI ESP

(A)	European American (EA)	African American (AA)	All (EA+AA)
PH1+PH2+PH3			
Allele Count (Alt/Ref)	68/8,515	14/4,371	82/12,886
Mutant Allele Frequency (%)	0.799	0.320	0.636
Prevalence (1 in)*	42,397	225,971	71,333
Carrier Frequency (1 in)*	63	156	79
PH1 (*AGXT*)			
Allele Count (Alt/Ref)	20/8,563	4/4,389	24/12,952
Mutant Allele Frequency (%)	0.234	0.091	0.185
Prevalence (1 in)	183,332	1,203,908	291,256
Carrier Frequency (1 in)	215	549	270

(B)	European American (EA)	African American (AA)	All (EA+AA)
PH1+PH2+PH3			
Allele Count (Alt/Ref)	85/8,550	18/4,385	103/12,936
Mutant Allele Frequency (%)	0.994	0.410	0.796
Prevalence (1 in)*	26,780	142,732	44,805
Carrier Frequency (1 in)*	51	122	63
PH1 (*AGXT*)			
Allele Count (Alt/Ref)	23/8,573	5/4,393	28/12,966
Mutant Allele Frequency (%)	0.268	0.114	0.216
Prevalence (1 in)	138,934	772,079	214,448
Carrier Frequency (1 in)	187	440	232

*P was determined by combining the individual prevalence of all PH types with bigenic PH cases counting as carriers.

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References

1. Rumsby, G: Primary Hyperoxaluria Mutation Database. http://www.uclh.nhs.uk/OurServices/ServiceA-Z/PATH/PATHBIOMED/CBIO/Pages/Phmdatabase.aspx, 2013.
2. Exome Variant Server: NHLBI GO Exome Sequencing Project (ESP), Seattle, WA (URL: http://evs.gs.washington.edu/EVS/) [date (01, 2014) accessed].
3. Gibbs, DA, Watts, RW: The variation of urinary oxalate excretion with age. *J Lab Clin Med,* 73**:** 901-908, 1969.
4. Stapenhorst, L, Sassen, R, Beck, B, Laube, N, Hesse, A, Hoppe, B: Hypocitraturia as a risk factor for nephrocalcinosis after kidney transplantation. *Pediatr Nephrol,* 20**:** 652-656, 2005.