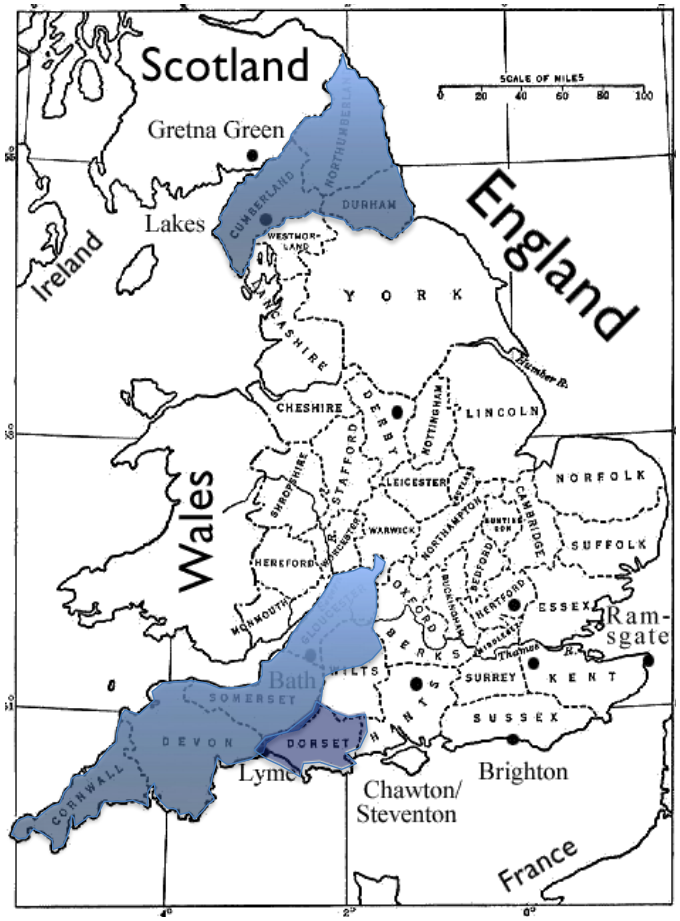
<u>Supplementary Figure 1:</u> Geographical distribution of United Kingdom cystinuria cohort.



Patients were recruited from the South West of England (including Southmead Hospital at North Bristol NHS Trust, Bristol Royal Hospital for Children, Dorset County Hospital, Royal Devon and Exeter Hospital and the Royal Cornwall Hospital) and the North East of England (including Newcastle Hospitals NHS Foundation Trust).

<u>Supplementary Table 1:</u> Seven patients suffered severe side effects of penicillamine

Side effects of penicillamine	**Frequency**
Elastosis serpignosa perforans	1
Dermopathy	2
Drug induced membranous nephropathy	1
Drug induced lupus	2
Albuminuria	1
Other (rash, nausea, migraine, leg pain, flank pain)	7

<u>Supplementary Table 2:</u> Genetic analysis and clinical characteristics, arranged by genotype

ID	Type		DNA variant and predicted protein description	Gender	Age at 1st stone event (y)	Age at diagnosis (y)	Delay in diagnosis (y)	Spont stones	Litho	Ops	Total stone events	Stone events per year	Stag-horn stone	24 hr cystine (latest) μmol/L[#]	eGFR	Current age	Rx
			SLC3A1														
1	**AA**	Com het	c.[161delC] (;) [exon 5-9 dup] p.[Gln55fs*51] (;) [exon 5-9 dup]	F	17	20	3	0	0	5	5	0.36		2130	71.4	31	pc, P
2	**AA**	Com het	c.[356dupA] (;) [1400T>C] p.[Glu120Glyfs*16] (;) [Met467Thr]	M	7	9	2	1	1	3	5	0.09		(239)	87	64	P
3	**AA**	Com het	c.[del exon 2-4] (;) [del exon 10]	M	21	21	0	0	2	3	5	0.28		_	96	39	P
4	**AA**	Com het	c.[647C>T] ; [Del 2-3] p.[Thr216Met] ; [Del 2-3]	F	19	20	1	7	1	1	9	0.31		(2069)	79.8	45	sb, T
5	**AA**	Com het	c.[647C>T] (;) [1578G>A] p.[Thr216Met] (;) [Trp526*]	M	25	42	17	20	7	5	32	1.10		4344	45	54	pc, sb
6	**AA**	Com het	c.[761A>C] (;) [c.1799G>A] p.[Asn254Thr] (;) [Gly600Glu]	F	21	21	0	15	0	4	19	3.17		1704 (3178)	86	27	
7	**AA**	Hom	c.[1093C>T] ; [1093C>T] p.[Arg365Trp] ; [Arg365Trp]	F	15	15	0	0	0	3	3	0.21		1295 (1209)	79	29	sb, T, lp
8	**AA**	Hom	c.[1136+2T>C] ; [1136+2T>C]	F	24	24	0	20	0	94	114	7.13		4065 (1307)	102	40	pc, T
9	**AA**	Com hom	c.[1332+2T>A] (;) [1372G>A] p.[?] (;) [Gly458Arg]	M	34	36	2	?0	0	4	4	1.33		3621 (3621)	68	37	
10	**AA**	Com het	c.[1354C>T] ; [exon 5-10 del] p.[Arg452Trp] ; [exon 5-10 del]	M	17	17	0	7	5	3	15	5		3262 (3754)	73	20	pc
11	**AA**	Com het	c.[1354C>T] (;) [exon 5-9 dup] p.[Arg452Trp] (;) [exon 5-9 dup]	M	34	34	0	0	0	3	3	0.07		4018 (966)	68	79	T, lp
12	**AA**	Com het	c.[1354C>T] (;) [1400T>C] p.[Arg452Trp] (;) [Met467Thr]	F	33	34	1	0	3	3	3	0.25		1500 (1534)	71.7	43	pc, T
13	**AA**	Com het	c.[1400T>C] (;) [exon 2 del] p.[Met467Thr] (;) [exon 2 del]	F	23	24	1	1		2	2	0.5		1542	>90	29	

ID	Type		DNA variant and predicted protein description	Gender	Age at 1st stone event (y)	Age at diagnosis (y)	Delay in diagnosis (y)	Spont stones	Litho	Ops	Total stone events	Stone events per year	Stag-horn stone	24 hr cystine (latest) μmol/L[#]	eGFR	Current age	Rx
14	**AA**	Com het	c.[1400T>C] (;) [exon 5-9 dup] p.[Met467Thr] (;) [exon 5-9 dup]	M	2	2	0	0	3	5	8	0.32	YES	540	88.5	27	pc, T
15	**AA**	Com het	c.[1400T>C] (;) [exon 5-9 dup] p.[Met467Thr] (;) [exon 5-9 dup]	F	11	18	7	90	2	14	106	2.72		2379 (1561)	87	50	P
16	**AA**	Com het	c.[1400T>C] (;) [exon 5-9 dup] p.[Met467Thr] (;) [exon 5-9 dup]	F	48	49	1	0	2	4	6	0.67	YES	2200 (1915)	>90	57	pc
17	**AA**	Com het	c.[1400T>C] (;) [exon 5-9 dup] p.[Met467Thr] (;) [exon 5-9 dup]	F	29	29	0	10	0	6	16	0.53		3600	65.3	59	pc
18	**AA**	Com het	c.[1400T>C] (;) [exon 5-9 dup] p.[Met467Thr] (;) [exon 5-9 dup]	F	16	54	38	?	0	1	1	NK		992	16	70	lp
19	**AA**	Hom	c.[1400T>C] ; [1400T>C] p.[Met467Thr] ; [Met467Thr]	F	16	57	41	1	0	5	6	0.13	YES	3330 (1437)	62.2	62	pc, T, lp
20	**AA**	Hom	c.[1400T>C] ; [1400T>C] p.[Met467Thr] ; [Met467Thr]	M	55	56	1	4	0	0	4	0.44		1862	>90	64	
21	**AA**	Com het	c.[1400T>C] (;) [1796T>C] p.[Met467Thr] (;) [Phe599Ser]	F	46	46	0	0	0	5	5	0.5		3534 (2673)	96	56	
22	**AA**	Hom	c.[1412C>G] ; [1412C>G] p.[Thr471Arg] ; [Thr471Arg]	M	25	27	2	?	2	6	>8	NK		2778 (1511)	97	43	sb, P
23	**AA**	Com het	c.[1975C>T] (;) [exon 5-9 dup] p.[Gln659*] (;) [exon 5-9 dup]	F	3	2	0	?	0	1	>1	NK		(2549)	111.4	35	pc, P
24 F1	**AA**	Hom	c.[2020dupT] ; [2020dupT] p.[Tyr674Leufs*20]; [Tyr674Leufs*20]	F	48	49	1	0	0	1	1	0.33		2469	89.7	51	P
25 F1	**AA**	Hom	c.[2020dupT] ; [2020dupT] p.[Tyr674Leufs*20]; [Tyr674Leufs*20]	F	20	23	3	0	0	3	3	0.08		_	85	58	sb, P
26	**AA**	Com het	c.[2020dupT] (;) [exon 5-9 dup] p.[Tyr674Leufs*20] (;) [exon 5-9 dup]	F	7	15	8	50	2	16	68	3.4		4070 (957)	61.2	27	sb, P
27	**AA**	Com het	c.[2020dupT] (;) [exon 5-9 dup] p.[Tyr674Leufs*20] (;) [exon 5-9 dup]	F	48	51	3	0	0	2	2	0.13		_	34	64	P, lp
			SLC7A9														

ID	Type		DNA variant and predicted protein description	Gender	Age at 1st stone event (y)	Age at diagnosis (y)	Delay in diagnosis (y)	Spont stones	Litho	Ops	Total stone events	Stone events per year	Stag-horn stone	24 hr cystine (latest) μmol/L[#]	eGFR	Current age	Rx
28 F2	**BB**	Hom	c.[313G>A] ; [313G>A] p.[Gly105Arg] ; [Gly105Arg]	M	29	29	0	2	0	0	2	0.12		(644)	77	46	T
29	**BB**	Com het	c.[313G>A] (;) [614dupA] p.[Gly105Arg] (;) [Asn206Glufs*3]	F	28	30	2	5	2	6	13	0.42		3284 (n/a Tx)	Tx	59	Tx
30	**BB**	Com het	c.[368C>T (;) 671C>T] p.[Thr123Met] (;) [Ala224Val]	M	42	42	0	0	9	5	14	0.88	YES	6504	>90	58	c
31	**BB**	Com het	c.[411_412delTG] (;) [614dupA] p.[Pro139Leufs*69] (;) [Asn206Glufs*3]	M	10	10	0	1	0	12	13	0.68		5305 (3095)	74	29	P
32	**BB**	Com het	c.[414_415delGC] (;) [exon 12 del] p.[Pro139Leufs*69] (;) [exon 12 del]	M	17	18	1	1-2 per y	3	11	34	2.62	YES	3147	80.9	30	pc, T
33	**BB**	Com het	c.[411_412del (;) exon 12 del] p.[Pro139Leufs*69] (;) [exon 12 del]	M	34	34	0	0	0	2	2	0.4		3277	>90	39	pc, T, lp
34	**BB**	Hom	c.[544G>A] ; [544G>A] p.[Ala182Thr] ; [Ala182Thr]	M	45	45	0	10	4	0	10	0.45		_	80	76	pc
35	**BB**	Com het	c.[544G>A] (;) [614dupA] p.[Ala182Thr] (;) [Asn206Glufs*3]	M	7	48	41	6	0	2	8	0.18		_	>90	52	
36	**BB**	Hom	c.[614dupA] ; [614dupA] p.[Asn206Glufs*3] ; [Asn206Glufs*3]	F	14	25	11	3	2	5	10	0.26		1662 (2062)	83**	52	P
37	**BB**	Hom	c.[614dupA] ; [614dupA] p.[Asn206Glufs*3] ; [Asn206Glufs*3]	F	16	29	13	20	0	2	22	0.44	YES	4381 (1677)	49.8	66	sb, P
38	**BB**	Hom	c.[614dupA] ; [614dupA] p.[Asn206Glufs*3] ; [Asn206Glufs*3]	M	41	41	0	2	0	2	4	0.09	YES	(3469)	18	86	
39	**BB**	Com het	c.[614dupA] (;) [1400-2A>G] p.[Asn206Glufs*3] (;) [splicing]	F	22	23	1	100	14	22	136	3.09		_	66	66	T, lp
40 F3	**BB**	Com het	c.[614dupA] (;) [exon 12 del] p.[Asn206Glufs*3] (;) [exon 12 del]	M	36	12	0	3	0	0	3	1		4602 (1978)	83	39	P, lp
41 F3	**BB**	Com het	c.[614dupA] (;) [exon 12 del] p.[Asn206Glufs*3] (;) [exon 12 del]	F	10	10	0	30	6	16	52	1.58	YES	_ (929)	27	43	sb, c, lp

ID	Type		DNA variant and predicted protein description	Gender	Age at 1st stone event (y)	Age at diagnosis (y)	Delay in diagnosis (y)	Spont stones	Litho	Ops	Total stone events	Stone events per year	Stag-horn stone	24 hr cystine (latest) μmol/L[#]	eGFR	Current age	Rx
42	**BB**	Hom	c.[671C>T] ; [671C>T] p.[Ala224Val] ; [Ala224Val]	M	24	24	0	0	2	5	7	0.24		_ (n/a Tx)	Tx	53	
43	**BB**	Com het	c.[671C>T] (;) [997C>T] p.[Ala224Val] (;) [Arg333Trp]	F	4	2	0	70	NK	15	85	4.47	YES	1630 (1500)	50	23	sb, T
44	**BB**	Com het	c.[671C>T] (;) [1369T>C] p.[Ala224Val] (;) [Tyr457His]	M	55	63	8	1	3	0	4	0.5		_	>90	63	
45	**BB**	Com het	c.[962G>A] (;) [1399+4_1399+7del] p.[Cys321Tyr] (;) [splicing]	F	19	19	0	>100	0	>6	~106	~13.25		2576 (1111)	90	27	P, lp
46	**BB**	Com het	c.[1399+4_1399+7del] (;) [exon 12del]	M	17	17	0	1-2/y	2	8	44	2	YES	4838 (2845)	>90	39	pc, T
47	**BB**	Com het	c.[1353C>A] (;) [1400-2A>G] p.[Tyr451*] (;) [splicing]	F	26	27	1	0	0	3	3	0.38		1317	35.9	34	pc, T
			SLC3A1 and SLC7A9														
48	**AAB**	Com het	*SLC3A1*: c.[exon 2-3 del] ; [exon 5-9 dup], *SLC7A9*: c.[544G>A] (;) [=] p.[Ala182Thr] (;) [=]	M	15	15	0	5	0	0	5	2.5		123* (598)	62	17	pc
49 F2	**BBA**	Hom + Com het	*SLC7A9*: c.[313G>A] ; [313G>A] p.[Gly105Arg] ; [Gly105Arg] *SLC3A1*: c.[1400T>C] (;) [=] p.[Met467Thr] (;) [=]	F	32	32	0	0	3	1	4	0.36		1258 (1258)	77.9	43	
50	**BBB**	Hom +Com het	SLC7A9: c.[544G>A;1060G>A] (;) [544G>A] p.[Ala182Thr;Ala354Thr] ; [Ala182Thr]	F	47	47	0	3	1	7	11	0.73	YES	1217	83.4	62	pc
			SLC3A1														
51	**A**	het	c.[761A>C] (;) [=] p.[Asn254Thr] (;) [=]	F	11	11	0	0	0	6	6	0.16		2144	60.9	48	pc
52	**A**	het	c.[exon 5-9dup] (;) [=]	F	25	53	28	2	0	1	3	0.1		2436 (2436)	70	55	lp
53	**A**	het	c.[exon 5-9dup] (;) [=]	M	19	25	6	2	0	2	4	0.07		_	14*** *	79	

ID	Type		DNA variant and predicted protein description	Gender	Age at 1st stone event (y)	Age at diagnosis (y)	Delay in diagnosis (y)	Spont stones	Litho	Ops	Total stone events	Stone events per year	Stag-horn stone	24 hr cystine (latest) μmol/L[#]	eGFR	Current age	Rx
54 F4	**A**	het	c.[exon 5-9dup] (;) [=]	M	9	27	18	1-2 per week	2	6	~3440	~78.2		2110	71.2	53	pc, c, T
55 F4	**A**	het	c.[exon 5-9dup] (;) [=]	F	13	13	0	0	2	3	6	0.11	YES	4072	65.1	57	pc, c
			SLC7A9														
56	**B**	het	c.[313G>A] (;) [=] p.[Gly105Arg] (;) [=]	M	17	23	6	1	0	1	2	0.33		112	>90	23	
57	**B**	het	c.[313G>A] (;) [=] p.[Gly105Arg] (;) [=]	F	24	28	4	0	2	2	4	0.8		2770	>90	29	lp, pc
58	**B**	het	c.[313G>A] (;) [=] p.[Gly105Arg] (;) [=]	F	17	18	1	5	0	0	5	0.25		1050	45.4	37	sb, c
59	**B**	het	c.[411_412del] (;) [=] p.[Pro139Leufs*69] (;) [=]	M	34	45	11	3	0	0	3	3		163*	63.7	45	lp
60	**B**	het	c.[544G>A] (;) [=] p.[Ala182Thr] (;) [=]	M	49	60	11	2	1	0	2	0.27		_	>90	60	-
61	**B**	het	c.[544G>A] (;) [=] p.[Ala182Thr] (;) [=]	M	62	71	9	0	2	0	2	0.22		_	>90	71	-
62	**B**	het	c.[614dupA] (;) [=] p.[Asn206Glufs*3] (;) [=]	M	43	45	2	3	0	0	3	1		1665	>90	46	-
63	**B**	het	c.[614dupA] (;) [=] p.[Asn206Glufs*3] (;) [=]	M	23	24	1	too many to count	2	17	many	NK		(3340)	61.8	44	pc, c, T
64	**B**	het	c.[614dupA] (;) [=] p.[Asn206Glufs*3] (;) [=]	M	39	46	7	5	5	3	10	1.63		_	>90	47	
65	**B**	het	c.[671C>T] (;) [=] p.[Ala224Val] ; [=]	M	25	25	0	1-2 per year	2	8	>12	~2.75		1980	>90	33	pc
66	**B**	het	c.[671C>T] (;) [=] p.[Ala224Val] (;) [=]	M	40	40	0	0	1	1	2	0.09	YES	5706	39.2	62	sb
67	**B**	het	c.[671C>T] (;) [=] p.[Ala224Val] (;) [=]	M	26	65	39	1 per year	0	0	40	~1		1676	69.6	66	
68	**B**	het	c.[671C>T] (;) [=] p.[Ala224Val] (;) [=]	M	17	18	1	0	0	2	2	0.07		1290	77.5	44	pc

ID	Type		DNA variant and predicted protein description	Gender	Age at 1st stone event (y)	Age at diagnosis (y)	Delay in diagnosis (y)	Spont stones	Litho	Ops	Total stone events	Stone events per year	Stag-horn stone	24 hr cystine (latest) μmol/L[#]	eGFR	Current age	Rx
69	**B**	het	c.[671C>T] (;) [=] p.[Ala224Val] (;) [=]	M	5	5	0	0	1	3	4	0.06	YES	2086	52.6	67	T
70	**B**	het	c.[1399+4_1399+7del] (;) [=]	M	35	35	0	3	0	6	9	2.25		568	>90	39	
71	**B**	het	c.[1399+4_1399+7del] (;) [=]	F	44	45	1	2	1	0	4	0.75		1277	83.3	48	
72	**B**	het	c.[exon 12 del] (;) [=]	M	24	24	0	too many to count	0	3	many	NK	YES	_ (n/a Tx)	Tx	61	
73	**?**		Nil detected with exon sequencing or MLPA	M	34	34	0	1-2 per year	4	3	>10	~2.08		1762	54.8	46	pc, T
74	**?**		Nil detected with exon sequencing or MLPA	M	16	16	0	1 per year	7	2	8	~2.29		2348	>90	23	pc, T
75	**?**		Nil detected with exon sequencing or MLPA	M	29	29	0	6 per year	0	1	>157	~6.04		3964	87.2	55	pc, c
76	**?**		Nil detected with exon sequencing or MLPA	M	54	54	0	2	3	0	5	0.83		578	82	60	–

Key/explanation of abbreviations used in table:

Rows highlighted in matching colours delineate groups of patients with identical genetic mutations. **ID** - where members of the same family are included, each family is denoted with a family identifier (e.g. F1, F2 etc.), **Hom**=homozygous (both alleles same mutation), **Com het** = compound heterozygote (2 different mutations detected, one in each allele), **het**=heterozygote (single mutated allele detected). **Delay in diagnosis** represents the time from a patient's first stone episode until the diagnosis of cystinuria was made. **Spont stones**=number of cystine stones passed spontaneously by patients not including stones passed after lithotripsy. **Litho**= number of lithotripsy sessions. **Ops**=number of operations to remove cystine stones (including open, percutaneous and endourological procedures). **24 hour cystine** stated as value on first testing i.e. off medication, and value in brackets refers to most recent value. [#]Units: 1000μmol/L is equivalent to 240mg/L, therefore to convert values given to mg/L divide by 4.161. For patients marked * the initial cystine measurement is spot cystine (units= μmol/mmol creatinine, normal range 3-17) patient 48 = 123, patient 59 = 163. **eGFR**=estimated glomerular filtration rate (ml/min/m^2) using abbreviated MDRD formulae, **=patient has congenital single kidney, ***=nephrectomy in 1953. **Tx**=renal transplant. **Rx** denotes medications currently prescribed – **lp**= low protein, **pc**=potassium citrate, **sb**=sodium bicarbonate, **P**=penicillamine, **T**=tiopronin. **NK** = not known, **n/a** = not applicable.