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Characterization of the Cystic Phenotype Associated with Monoallelic *ALG8* and *ALG9* Pathogenic Variants

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Key Points

- Loss-of-function *ALG8* and *ALG9* variants were enriched in polycystic kidney/liver groups and International Classification of Diseases–coded cystic individuals in population cohorts.
- The ALG8 and ALG9 kidney phenotypes were usually mild to moderate, and lower eGFR or kidney failure was rare.
- *ALG8* pathogenic variants sometimes resulted in severe polycystic liver disease.

Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) is a common, inherited nephropathy often resulting in kidney failure. It is genetically heterogeneous; along with the major genes, *PKD1* and *PKD2*, at least eight others have been suggested. *ALG8* pathogenic variants have been associated with autosomal dominant polycystic liver disease and implicated in ADPKD, while *ALG9* has been suggested as an ADPKD gene, but details of the phenotypes and penetrance are unclear.

Methods We screened >3900 families with cystic kidneys and/or livers using global approaches to detect *ALG8* or *ALG9* pathogenic variants. In addition, population cohorts with sequence data (Genomics England 100K Genomics Project, UK Biobank, and Mayo Clinic Biobank [MCBB]) were screened for *ALG8*/*ALG9* pathogenic variants.

Results Multicenter screening of individuals with polycystic kidney and/or liver disease identified 51 (1.3%) ALG8 (7 multiplex) and 23 (0.6%) ALG9 (5 multiplex) families—frequencies that were approximately 10× and approximately 24× greater than nonpolycystic kidney disease controls. Analysis of individuals with polycystic kidney disease phenotypes in 100K Genomics Project, UK Biobank, and MCBB identified nine ALG8 (0.39%) and nine ALG9 (0.39%) families, an enriched frequency over controls. Two individuals had *PKD1* and *ALG8* pathogenic changes. Eighty-nine percent of individuals with ALG8 mutations with imaging in the entire MCBB had kidney cysts (50%, >10 cysts), with greater median kidney and liver cyst numbers than controls. For ALG9, 78% had kidney cysts (27%, >10 cysts). Individuals with ALG8 mutations typically had mild cystic kidneys with limited enlargement. Liver cysts were common (71%), with enlarged livers (>2L) found in 11 of 62 patients, although surgical intervention was rare. The ALG9 kidney phenotype was also of mild cystic kidneys, but enlarged livers were rare; for both genes, CKD or kidney failure were rare.

Conclusions *ALG8* and *ALG9* are defined as cystic kidney/liver genes but with limited penetrance for lower eGFR.

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Introduction

Polycystic kidney diseases (PKDs) are a group of inherited disorders that result in kidney cyst development and often kidney failure. The most common form is autosomal dominant PKD (ADPKD), characterized by progressive cyst development and growth resulting in enlarged kidneys in adulthood and typically kidney failure in late middle age.[1–3] Imaging cyst number criteria by ultrasound or MRI have been established to diagnose or exclude the disease.[4,5] Estimates of the prevalence vary, with values of approximately 1/1000 for clinically significant disease and higher levels for more limited cystic kidneys.[6–8] ADPKD causes 5%–10% of kidney failure worldwide (5.1% in the United States).[9] Liver cysts occur in most patients as they age with severe polycystic liver disease, requiring surgical resection or transplantation, occurring in a small minority of mainly female patients.[3,10] The related but much rarer autosomal dominant polycystic liver disease (ADPLD) is characterized by multiple liver cysts, sometimes symptomatic, but with no or few kidney cysts.[11]

The major genes for ADPKD are *PKD1* and *PKD2* (encoding polycystin 1 and polycystin 2, respectively) that account for approximately 78% and approximately 15%, respectively, of the clinical ADPKD population.[12] ADPKD-*PKD1* is a more severe disease, with a median age at onset of kidney failure of 58.0 years compared with 74.8 years for ADPKD-*PKD2*.[12] Allelic effects for *PKD1* (truncating or nontruncating pathogenic variants) are also associated with the age at kidney failure (55.1 and 65.8 years, respectively).[12,13] Polycystin 1 and polycystin 2 form a complex, and a likely pathogenic site associated with PKD is the primary cilium, a signaling antenna found on most cells.[14,15] The major ADPLD genes are *PRKCSH* (encoding glycosidase IIβ; GIIβ) and *SEC63* (encoding the protein translocation subunit, SEC63) that likely account for most severe cases.[11] GIIβ and SEC63 are located in the endoplasmic reticulum and involved in glycosylation, folding, trafficking, and quality control of plasma membrane and secreted proteins.[16] Disruption of efficient trafficking of the polycystin complex with reduced GIIβ or SEC63 is a likely cause of cyst development.[17]

Eight additional genes have been suggested to cause a monoallelic ADPKD-like phenotype; six of these encode endoplasmic reticulum–resident, proteostasis proteins: *ALG5*,[18] *ALG6*,[19] *ALG8*,[20] *ALG9*,[21] *DNAJB11*,[22] and *GANAB*,[23] plus the ciliogenesis genes, *IFT140* and *NEK8*.[24,25] Each has a distinctive phenotype and varying levels of evidence as an ADPKD spectrum gene. Both *DNAJB11* and *ALG5* are associated with kidney failure on average at approximately 75 years because of fibrosis of nonenlarged kidneys,[18,26] while the risk of kidney failure seems low for the other genes. *IFT140* results in kidney enlargement due to a limited number of large cysts.[24] For *GANAB* and *ALG6*, the kidney disease is mild and the liver disease can predominate, even presenting as severe ADPLD.[19,23,27] Together, these genes likely account for a few percent of total families with ADPKD, partially explaining individuals without *PKD1* or *PKD2* pathogenic variants.[8]

Biallelic *ALG8* pathogenic variants are associated with the congenital disorder of glycosylation (CDG) type Ih,[28] whereas biallelic *ALG9* variants have been associated with CDG type Il,[29] as well as Gillessen–Kaesbach–Nishimura skeletal dysplasia.[30] The first evidence of cyst development associated with *ALG8* was enrichment of predicted loss-of-function variants in ADPLD populations compared with controls.[27] These individuals had many small or large liver cysts, but 80% also had a few kidney cysts. A more recent study found enrichment of predicted loss-of-function *ALG8* variants in a cystic kidney cohort identified by International Classification of Diseases (ICD) codes.[20] In 26 ALG8 individuals with imaging available, 19 (73%) had ≥4 kidney cysts and 18 (69%) had bilateral cysts, higher than a control group, but liver cysts were not enriched. In a screen of 920 Taiwanese families with ADPKD, six had *ALG8* predicted loss-of-function variants, some with atypical cystic kidney disease.[31] A recent study described a large ADPLD-*ALG8* family.[30] However, ALG8 family data are limited, and predicted loss-of-function *ALG8* variants are quite common in normal populations,[32] so the penetrance of predicted loss-of-function variants to cause a cystic phenotype is unclear. *ALG9* has been defined as an ADPKD spectrum gene from screening 122 patients with ADPKD without *PKD1* or *PKD2* pathogenic variants that identified two with heterozygous *ALG9* loss-of-function variants.[21] In addition, a screen of 92,455 exomes of a population-based cohort identified 21 with rare predicted loss-of-function *ALG9* variants.[21] Seven of 11 (64%) with abdominal imaging had five or more kidney cysts. In a PKD gene panel screen of 100 German patients with ADPKD, one had a *ALG9* predicted loss-of-function variant.[33] Limited family data are available for ALG9 individuals, and the full extent of the phenotype/penetrance is unclear.

In this study, we screened individuals with a cystic kidney and/or liver phenotype for *ALG8* or *ALG9* pathogenic/likely pathogenic (P/LP) variants. In addition, cystic cohorts in the England 100K Genomics Project (100kGP), UK Biobank (UKBB), and Mayo Clinic Biobank (MCBB) populations, plus all MCBB participants, were screened for P/LP variants to these genes and the phenotype characterized.

Methods

Study Participants and Clinical Analyses

Families with *ALG8* and *ALG9* P/LP variants or high-suspicion variants of uncertain significance (VUS) were identified at various screening sites in a population with a cystic kidney and/or liver phenotype in part 1 of the study (Figure 1A). The number of individuals identified in clinical trial populations were HALT-PKD (*ALG8*, n=1; *ALG9*, n=2; total n=981), DIPAK (*ALG8*, n=1; *ALG9*, n=1), and TAME PKD (*ALG9*, n=1; total n=93). Families were either previously Sanger screened for *PKD1* and *PKD2* and negative or naïve to testing. In part 2, ALG8 and ALG9 probands were identified in cystic kidney groups in the 100kGP, UKBB, and MCBB cohorts (Figure 1B). Part 3 analyzed ALG8 and ALG9 individuals in the whole MCBB cohort (Figure 1C).

The relevant institutional review boards or ethics committees approved all studies, and participants gave informed consent. Clinical and imaging data for parts 1 and 3 were obtained by review of the electronic health

record (EHR). Hypertension was recorded at the age of diagnosis or when two or more consecutive readings were >140/90. Total kidney volume (TKV) was calculated semiautomatically from the latest available computed tomography or MRI[34] before kidney failure, and the Mayo Imaging Class (MIC) was determined.[35] Cyst number was counted by manual inspection of images, and cysts >2 mm were recorded. Parapelvic cysts were excluded from the count. eGFR was calculated from the most recent clinical serum creatinine measurements with the CKD Epidemiology Collaboration creatinine equation (2021).[36]

Blood or buccal samples for standard DNA isolation were collected from probands and available family members. The genetic screening and variant analysis pipelines were similar to that described,[24] but more details are provided for each population (Supplemental Methods). The transcripts used for variant description were *ALG8*, GenBank: NM_024079 and *ALG9*, GenBank: NM_024740. Frequencies of variants are shown in the gnomAD v4.1.0 or v3.1.2 databases for the entire populations.

An unpaired *t* test was used for two-group comparisons, and Mann–Whitney *U* test was used to compare cyst counts between individuals and their age- and sex-matched controls. In the analysis of the UKBB and 100kGP data, *P* values are calculated using chi-squared tests with Yates's correction. Regression analysis was used to compare slopes of eGFR and TKV populations.

Further details of the clinical and genetic analyses of the study populations are provided in the Supplemental Methods.

Results

Part 1: Analysis of a Clinical Cystic Kidney and/or Liver Cohort for Monoallelic *ALG8* Pathogenic Variants

In part 1 of the study, 3935 families with kidney and/or liver cysts, some involved in ADPKD clinical studies, were screened by research or clinical testing using a targeted next-generation sequencing gene panel, whole-exome sequencing (WES), or whole-genome sequencing at six different sites (Figure 1A). From this analysis, seven multiplex and 44 singleton ALG8 families (total 51) and five multiplex and 18 singleton ALG9 families (total 23) were identified.

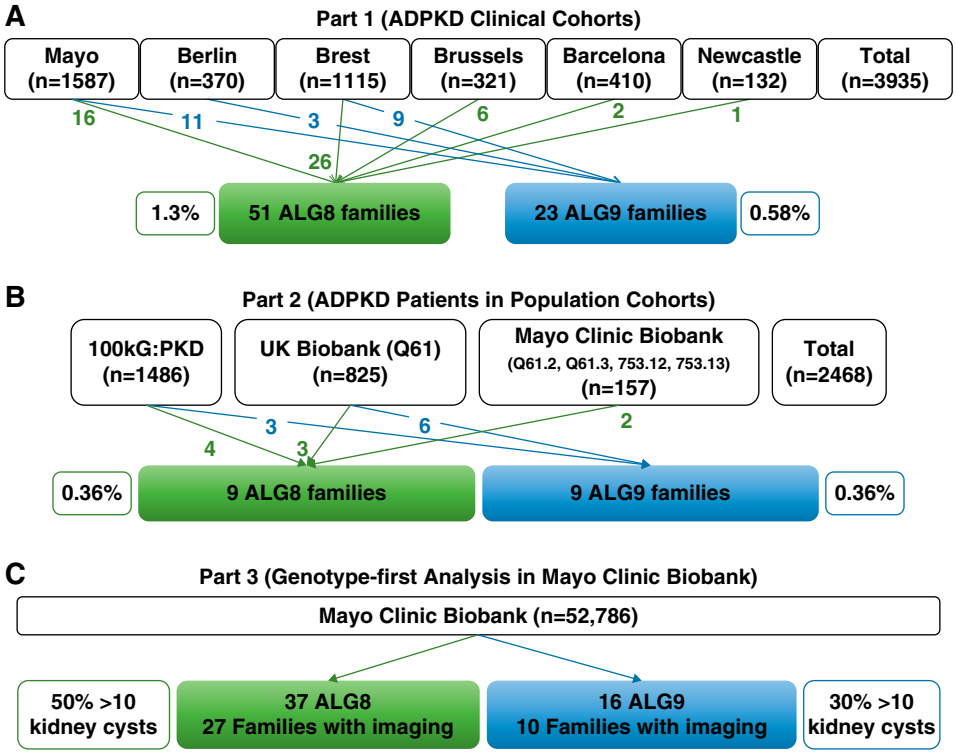

Figure 1. Details of the study design. The study was divided into screening of ADPKD spectrum families (A; part 1), analysis of cystic kidney disease cohorts identified in previously sequenced populations (B; part 2), and analysis of all ALG8 and ALG9 individuals in MCBB (C; part 3). (A) Part 1 included participants from a range of clinical and observational studies (see Methods and Supplemental Methods for details) and sequenced at the six indicated sites (total *n*=3935); the number of ALG8 and ALG9 families identified at each site and in total are indicated. ALG8 represented 1.3% and ALG9 0.58% of these PKD/polycystic liver disease cohorts. (B) Part 2 populations consisted of the England 100K Genome Project Cystic Kidney Disease cohort (100kGP:PKD), UKBB individuals with ICD-10 Q61 code, and the MCBB ADPKD cohort identified with the indicated ICD-9 and ICD-10 codes and confirmed as ADPKD. The number of analyzed individuals and detected ALG8 and ALG9 probands per study site is indicated with overall 0.36% ALG8 and 0.36% ALG9. (C) In part 3, all MCBB families with P/LP *ALG8* and *ALG9* variants identified are indicated along with the number of families with imaging data. In this cohort, 50% and 30% of ALG8 and ALG9 individuals had >10 kidney cysts, respectively. 100kGP, 100K Genomics Project; ADPKD, autosomal dominant polycystic kidney disease; ICD, International Classification of Diseases; MCBB, Mayo Clinic Biobank; PKD, polycystic kidney disease; P/LP, pathogenic/likely pathogenic; UKBB, UK Biobank.

Multiplex Families

Seven multiplex families, including 18 individuals (Table 1) with two or more members with predicted loss-of-function *ALG8* variants, were identified (see Figure 2 and legend for details; Table 2). No family had another clear cause of the cystic phenotype, but some possible modifier variants were identified (Figure 2 and Supplemental Table 1). A total of six patients (33%) had eGFR <60 ml/min per 1.73 m^2, including one patient with kidney failure at age 73 years (Table 1).

Singletons

In addition, 44 singletons with a clinically confirmed cystic phenotype and an *ALG8* P/LP variant were identified (Table 2, Supplemental Figure 1, and Supplemental Table 2). The pathogenic variants were predicted loss of function in 42 individuals and missense in two. Two other individuals had *ALG8* missense variants classified as VUS but were not included in the analyses. No individual had a clearly pathogenic variant in another ADPKD gene, but possible modifier variants were documented in five cases (Supplemental Tables 1 and 2). Most of these individuals did not have a known PKD or polycystic liver disease family history, although five had a likely affected relative(s), but a sample to test segregation and detailed clinical data were not available (Supplemental Table 2). A total of 12 singleton patients (27%) had an eGFR <60 ml/min per 1.73 m^2, including two patients with kidney failure (Supplemental Table 2).

ALG8 as a Possible Phenotypic Modifier

In two families, an *ALG8* pathogenic change was found with a *PKD1* P/LP variant. PK200618 had *ALG8* p.Arg364* but also the LP *PKD1* missense variant p.Trp3195Arg (Supplemental Table 1). They had severe PKD with an eGFR=10 ml/min per 1.73 m^2 at age 44 years with both kidneys approximately 20 cm in length and some liver cysts (Supplemental Figure 3). One brother had kidney failure at age 48 years, but genetic analysis of him or other family members was not possible. A second individual recruited from the 100kGP:PKD cohort (UK6) had enlarged kidneys with multiple cysts but normal kidney function at age 34 years and *ALG8* c.1296dup (Supplemental Table 1) plus *PKD1* p.Gln4231*.

Part 1: Analysis of a Clinical Cystic Kidney and/or Liver Cohort for Monoallelic *ALG9* Pathogenic Variants

Multiplex Families

We identified five multiplex families, including 14 affected individuals (see Figures 1 and 3 and legend for details, Tables 1 and 2). Three patients (21%) had an eGFR <60 ml/min per 1.73 m^2, with none having kidney failure (Table 1).

Singletons

Eighteen singletons with *ALG9* P/LP variants were also detected (Figure 1, Table 2, Supplemental Figure 2, and Supplemental Table 3). Seven patients (39%) had an eGFR <60 ml/min per 1.73 m^2, including two with kidney failure (Supplemental Table 3).

Part 2: Analysis of Individuals with Cystic Kidney Defined in Population Cohorts

To determine the burden of predicted loss-of-function *ALG8* and *ALG9* variants more broadly, we analyzed genetic and clinical data from the 100kGP:PKD cohort, UKBB individuals coded for ADPKD (Q61), and MCBB individuals with ADPKD ICD codes (Figure 1B).

England 100k Genomes Project (100kGP) Analyses

Whole-genome sequencing screening of 1486 individuals from a broadly selected cystic kidney and/or liver group (100kGP:PKD; see Figure 1B and Supplemental Methods for details) and 28,778 from an intellectual disability (control) cohort detected six (0.4%) and 44 (0.15%) individuals, respectively, with predicted loss-of-function *ALG8* variants. In the 100kGP:PKD group, UK6 also had a *PKD1* pathogenic variant (see above) and one was a relative (Table 2 and Supplemental Table 4). For *ALG9*, three (0.2%) probands were in the 100kGP:PKD and 15 (0.05%) in the control group (Table 2 and Supplemental Table 4). Comparison of the frequency of individuals with predicted loss-of-function *ALG8* and *ALG9* variants in the genetically unresolved 100kGP:PKD and control groups showed a significant enrichment for both gene groups in the PKD cohort (see Figure 4A for details).

UKBB

In 334,701 individuals with WES data in the UKBB,[37] 825 had the ICD-10 code Q61 (ADPKD) and 7425 had the ICD-10 code N28 (other disorders of kidney and ureter). Screening for individuals with rare (minor allele frequency: ≤0.1%) predicted loss-of-function variants showed the strongest association between Q61 and *ALG9* (0.7% among Q61 cases versus 0.03% among Q61 controls, $P < 0.001$), but only marginally significant in the N28 group ($P = 0.048$; see Figure 4B for details). Rare predicted loss-of-function variants in *ALG8* were also significantly associated with the Q61 and N28 cases versus controls (both $P = 0.03$; see Figure 4B for details).

Analysis of Patients with ADPKD Identified within MCBB

Using ADPKD ICD-9 and -10 codes (see Supplemental Methods for details) and manual inspection of EHR of individuals with abdominal imaging, 157 individuals with an ADPKD diagnosis were identified (Figure 1C). WES identified two individuals with *ALG8* P/LP variants; one ALG8 individual also had a *PKHD1* predicted loss-of-function variant, a known cause of kidney and liver cysts[27,38] (Table 2 and Supplemental Tables 1 and 5).

Part 3: Analysis of the Whole MCBB Population for *ALG8* and *ALG9* P/LP Variants

In the MCBB cohort (n=52,786), approximately 70% had abdominal imaging and all had WES. The sequence data revealed 37 and 16 individuals with *ALG8* and *ALG9* P/LP variants, including 28 (27 families) and 10 with imaging data, respectively (Figure 1C, Table 2, Supplemental Figures 4 and 5, and Supplemental Table 5). Two ALG8 individuals had >40 kidney cysts and an ADPKD diagnosis (part 2), and 14 had ≥10 cysts, including one with ICD-9 code 753.10, but no kidney or liver cysts were detected in two patients (Figure 5A). To determine

Table 1. Details of families with *ALG8* or *ALG9* pathogenic variants

Demographics					Clinical Details			Abdominal Imaging									Other Details
Pedigree (Study)	Pathogenic Variant	Participant	Sex	Race	Dx, Age (yr)	eGFR, Age (yr)	Hypertension Age (yr)	Type	Age (yr)	Kidney Cysts	RKV (ml)	LKV (ml)	TKV (ml)	MIC	Liver Cysts	TLV (ml)	Fig	
ALG8																		
M1021 (Mayo)	c.1090C>T (p.Arg364*)	I-1	M	W	AbP, 81	55, 82	Y, 82	CT	82	~35LK, ~15RK	215	254	469	2A	Nu	1624	2B	—
		II-2	F	W	AbP, 38	78, 61	Y, 59	CT	61	BNu	398	276	674	1B	N	1273	2C	PulNod
		II-3	M	W	LFlP, 49	79, 57	N	CT	52	~50LK, ~10RK	276	316	592	1B	Nu	1463	2D	
		II-4	M	W	AbP, 49	98, 52	N	MR	52	~25LK, ~15RK	235	257	492	1A	Nu	1985	2E	—
M1073 (Mayo)	c.1090C>T (p.Arg364*)	II-2	M	W	LK Bl, 38	KF, 73	Y, 38	CT	67	BNu	220	414	634	1A	N	1395	2G	LuCaG, AdCa, *PKD1* p.Asn1867Ser
		II-3	F	W	Screen, 59	66, 63	Y, 53	CT	62	4EK	129	119	248	1A	Nu	1172	2H	ArCa
P907 (Oviedo)	c.705del (p.Phe235Leufs*13)	I-1	M	W	Screen, ?	NA	Y, 67	NA	—	BM S	—	—	—	—	NA	—	—	Alz (73 yr), *NPHP1* p.Ser566?
		II-1	F	W	Screen, ?	45, 65	Y, 65	NA	—	3LK, 5RK	—	—	—	—	MS	—	—	*NPHP1* p.Ser566?, *INVS* p.Glu903?
		II-4	F	W	Screen, ?	50, 56	Y, ?	US	56	2LK	—	—	—	—	NA	—	—	*NPHP1* p.Ser566?
		II-5	F	W	LK At, 36	52, 58	Y, 27	NA	—	At LK, MS RK	—	—	—	2B	MS	—	—	*NPHP1* p.Ser566?, *INVS* p.Glu903?
1P (Brussels)	c.(369_546)del (Cys124Lysfs*23) (deletion of ex 4)	II-1	F	W	Screen, 49	59, 74	N	CT	72	2LK, 1Lg RK	355	138	493	2A	Nu Lg	1656	2K	—
		II-2	M	W	Inc, 33	76, 62	Y, 33	MR	61	BM Lg Ex	568	884	1452	2A	Nu S	1860	2L	KC He (57 yr)
2VR (Brussels)	c.1501del (p.Val501*)	I-1	F	W	Screen, 40	70, 55	N	MR	50	5LK, 3RK	145	173	318	1A	>50 S	—	2N	—
		II-1	M	W	AbP, 20	124, 29	N	MR	29	>6EK	180	245	425	1A	N	1835	2O	—
PK200583 (Brest)	c.1090C>T (p.Arg364*)	I-1	M	W	Inc, 52	>90, 52	N	CT	52	BM S 1Lg	166	139	305	—	~10 S	—	2Q	—
		II-1	F	W	AbP, 18	131, 21	N	CT	21	~15 EK	160	221	381	—	N	—	2R	AlbU, Sco
PK200301 (Brest)	c.535C>T (p.Arg179*)	I-2	M	W	NA	NA	N	NA	—	BM	—	—	—	—	F	—	—	—
		II-1	M	W	Hem, 12	132, 17	N	CT	17	8RK, 11LK	233	226	459	—	N	—	2T	NL

Demographics					Clinical Details			Abdominal Imaging									Other Details
Pedigree (Study)	Pathogenic Variant	Participant	Sex	Race	Dx, Age (yr)	eGFR, Age (yr)	Hypertension Age (yr)	Type	Age (yr)	Kidney Cysts	RKV (ml)	LKV (ml)	TKV (ml)	MIC	Liver Cysts	TLV (ml)	Fig	
ALG9																		
M157 (Mayo)	c.1219C>T (p.Arg407*)	III-3	M	W	NA	73, 68	N	CT	67	BM	—	—	—	—	1	—	3F	DCM
		IV-1	F	W	NA	70, 58	NA	MR	57	BF Ex	—	—	—	—	N	—	3B	—
		IV-2	M	W	Screen, ?	65, 56	NA	CT	47	BF	—	—	—	—	N	—	3C	—
		IV-5	F	W	Screen, ?	66, 67	Y, <61	US	61	7B	—	—	—	—	N	—	—	—
		IV-6	F	W	Nd	35, 64	Y	CT	61	14LK, 4RK	208	206	414	1A	1	2127	3D	DCM
		IV-9	M	W	Screen, ?	93, 58	Y, 52	MR	43	2LK, 2RK	167	198	365	1A	N	—	3E	—
M242 (Mayo)	c.309_328del (p.Trp103Cysfs*25)	I-1	M	W	Screen, ?	66, 70	N	US	69	B	—	—	—	—	Nu	—	—	—
		II-1	M	W	Prt, 26	137, 33	N	CT	26	17LK, 18RK	243	230	473	1B	N	1698	3J	—
M1328 (Mayo)	c.530T>A (p.Leu177*)	I-1	M	W	NA	NA	NA	US	70	BF	—	—	—	—	1 Lg	—	—	PNeph
		II-1	F	W	Nd	109, 37	N	MR	36	10LK, 8RK	212	213	425	1B	N	—	3L	—
PK14053 (Brest)	c.119_131+17del (p.Glu40fs)	II-1	F	W	NA	53, 60	Y, ?	CT	60	BM	255	220	475	1A	N	—	3N	BrCa, HyCa, OvC
		II-2	F	W	NA	28, 66	Y, ?	US	66	B	380	615	995	1B	N	—	—	
PK14505 (Brest)	c.327T>G (p.Tyr109*)	I-2	F	W	NA	>90, ?	Y, ?	MR	55	1LK, 1RK	—	—	—	NA	MS	—	3P	—
		II-1	M	W	HTN, ?	>60, 21	Y, ?	MR	21	BNu	491	606	1097	1E	NA	—	3Q	*PKHD1* p.Met1fs

AbP, abdominal pain; AdCa, adrenal carcinoma; AlbU, albuminuria; Alz, Alzheimer; ArCa, arterial calcification; At, atrophy; B, bilateral; BF, bilateral few; Bl, bleeding; BM, bilateral multiple; BNu, bilateral numerous; BrCa, breast cancer; Car, carotid; CT, computed tomography; DCM, dilated cardiomyopathy; Dx, diagnosis reason; Dx, Age, diagnosis reason and age; EctP, ectopic pregnancy; EK, each kidney; Ex, exophytic; F, few; Fig, figure; He, hemorrhagic; Hem, hematuria; HTN, hypertension; HyCa, hypercalcemia; Inc, incidental during imaging; KC, kidney cyst; KF, kidney failure; LFlP, left flank pain; Lg, large; LK, left kidney; LKV, left kidney volume; LuCaG, lung calcified granuloma; MIC, Mayo Imaging Class; MR, magnetic resonance; MS, multiple small; N, normal; NA, not available; Nd, never diagnosed; NL, nephrolithiasis; Nu, numerous; OvC, ovarian cysts; PNeph, partial nephrectomy; Prt, proteinuria; Pul Nod, pulmonary nodule; Pyl, pyelonephritis; RK, right kidney; RKV, right kidney volume; S, small; Sco, scoliosis; Screen, screening; TKV, total kidney volume; TLV, total liver volume; U, Unknown; W, White; ?, age not available; ~, approximately.

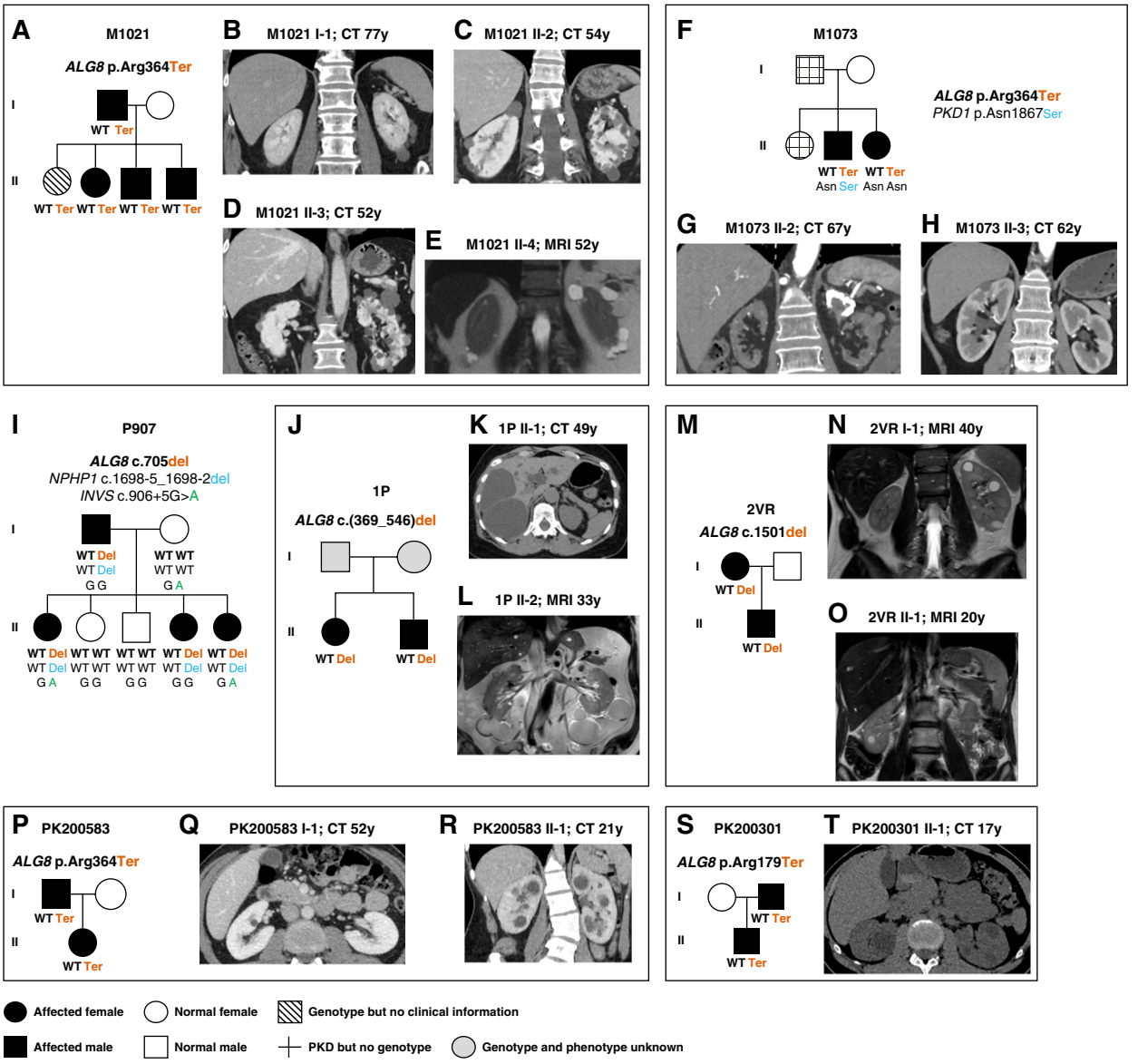

Figure 2. Pedigree and imaging details of seven multiplex ALG8 families. (A–E) Pedigree M1021: Four individuals in two generations had bilateral kidney cysts, some predominating in the left kidney, all apart from II-2 had liver cysts, and all had the *ALG8* nonsense variant, p.Arg364*. Kidney function was normal except for I-1 with mildly lower eGFR (Table 1). II-1 also had the *ALG8* variant, but no clinical information was available. (F) Pedigree M1073: II-2 and II-3 had the *ALG8* variant p.Arg364*, but very different disease courses (Table 1). (G) II-2 presented with abdominal pain and had multiple kidney cysts and kidney failure at age 73 years. (H) II-3 had just a few kidney and liver cysts, detected during donor evaluation, and normal kidney function. The father (I-1) had a diagnosis of PKD, and the sister (II-1) had a single cyst at age 69 years, but samples were not available. II-2 but not II-3 had the *PKD1* VUS, p.Asn1867Ser (Supplemental Table 1). (I) Pedigree P907: Described unlinked to *PKD1* or *PKD2*[47] and without a pathogenic variant in these genes,[48] had the *ALG8* deletion, c.705del in the father and three daughters. I-1, II-1, and II-5 had multiple cortical cysts, while II-5 also had left kidney atrophy. Reanalysis of II-4 by ultrasound at age 40 years identified two left kidney cysts. Two other LP recessive variants in the ciliopathy genes, *NPHP1* and *INVS*, were detected (Supplemental Table 1). (J) Pedigree 1P: Two siblings had an *ALG8* exon 4–5 deletion. (L) II-2 was diagnosed incidentally with several large exophytic kidney cysts and numerous small liver cysts. (K) II-1 had three kidney and several large liver cysts, and the family history was uncertain. (M and O) Pedigree 2VR: II-1 presented with abdominal pain at age 20 years, and bilateral kidney cysts were detected on imaging, and an *ALG8* deletion, c.1501del identified. (N) The mother also had kidney cysts and the *ALG8* variant. (P) Pedigree PK200583: I-1 and II-1 had the *ALG8* nonsense variant, p.Arg364*. (Q and R) II-1 presented with abdominal pain and PKD diagnosed on imaging at 18 years; subsequently, I-1 was found to have kidney and liver cysts. (S and T) Pedigree PK200301: II-1 presented with hematuria at 12 years, and cysts and the *ALG8* variant, p.Arg179*, were identified. The father had the variant and bilateral kidney and a few liver cysts. The key indicates the significance of shading. Only affected individuals or others with genetic and/or clinical information available are shown. The type and age at imaging are shown. LP, likely pathogenic; VUS, variants of uncertain significance.

Table 2. Details of the *ALG8* or *ALG9* pathogenic variants and significant VUS

cDNA Change	Protein Change	Type	Effect	GnomAD v4.1.0	First Publication	ClinVar	ACMG Designation	Pedigree
ALG8								
c.95+1G>A	p.Tyr32?	Splice	Truncating	3.85e-6	No data	2× LP	P	*M2226*
c.121C>T	p.Arg41*	Nonsense	Truncating	2.91e-5	No data	3× P	P	M1339, 4N, PK210778, *UK3*
c.164G>A	p.Trp55*	Nonsense	Truncating	1.37e-6	No data	No data	LP	*M2195*, *M2210*
c.210_213del	p.Phe70Leufs*20	FS del	Truncating	0	No data	No data	LP	PK210686
c.368+2T>G	p.Glu123?	Splice	Truncating	9.91e-6	[43]	2× LP	P	*M2202*, *M2221*
c.(369_546)del	p.Cys124Lysfs*23	Large del	Truncating	1.20e-6	No data	No data	LP	1P
c.535C>T	p.Arg179*	Nonsense	Truncating	3.55e-5	[27]	2× P	P	M1417, 5, PK200301, PK210254, B-0902
c.546+1G>A	p.Lys182?	Splice	Truncating	0	No data	No data	LP	PK210605
c.547-2A>G	p.Lys183?	Splice	Truncating	0	No data	No data	LP	M1898
c.643C>T	p.Arg215*	Nonsense	Truncating	5.47e-6	No data	No data	LP	*M2152*
c.673G>A	p.Asp225?	Splice	NTrunc	1.24e-6	No data	No data	LP	PK210204
c.(674_898)del	p.Asp225_Ile299del	Large del	Truncating	0	No data	No data	LP	6V
c.705del	p.Phe235Leufs*13	FS del	Truncating	0	No data	No data	P	P907
c.685C>T	p.Arg229*	Nonsense	Truncating	2.87e-5	No data	2× P	P	M2273, *M2197*, *M2227*
c.777+1G>A	p.Asn260?	Splice	Truncating	2.97e-6	No data	1× LP	LP	PK210526
c.777+2T>C	p.Asn260?	Splice	Truncating	0	No data	No data	LP	*M2201*
c.824del	p.Gly275Alafs*27	FS del	Truncating	3.84e-6	No data	No data	P	PK5270
c.867C>G	p.Tyr289*	Nonsense	Truncating	0	No data	No data	LP	*M2280*
c.898+1G>T	p.Gly300?	Splice	Truncating	1.37e-6	No data	No data	LP	*M2209*
c.964C>T	p.Gln322*	Nonsense	Truncating	0	No data	No data	LP	M1290
c.981dup	p.Val328Serfs*28	FS del	Truncating	3.04e-5	[43]	1× P	P	M1792, *M2151*, *M2225*
c.1038+1G>T	p.Pro347?	Splice	Truncating	2.15e-4[a]	[27]	1× P	P	M346, *M2222*
c.1041del	p.Ser348Leufs*19	FS del	Truncating	3.10e-6	No data	No data	LP	*UK5*
c.1049del	p.Phe350Serfs*17	FS del	Truncating	0	No data	No data	LP	PK210289
c.1057del	p.Trp353Glyfs*14	FS del	Truncating	1.97e-5	No data	No data	LP	PK210575
c.1090C>T	p.Arg364*	Nonsense	Truncating	8.24e-5	[43]	9× P, 2× LP	P	B-0922, M1021, M1073, M1634, P1498, PK2721, PK5155, PK150294, PK160389, PK170747, PK190196, PK191040, PK200583, PK200618, PK210884, PK210329, PK200618, NEW1, *M2200*, *M2223*, *M2198*, *M2150*, *M2192*, *M2229*, *M2218*, *NC*, *UK1*, *UK4*
c.1114dup	p.Ser372Lysfs*11	FS del	Truncating	1.20e-6	No data	No data	LP	M849
c.1134G>A	p.Trp378*	Nonsense	Truncating	0	No data	No data	LP	M1076, PK3148
c.1179-2A>G	p.Ser393?	Splice	Truncating	6.00e-6	No data	No data	LP	M2174
c.1218del	p.Leu407*	Nonsense	Truncating	7.51e-6	No data	No data	LP	PK210567, *M2205*, *M2216*, *M2232*
c.1276+2T>C	p.Glu426?	Splice	Truncating	0	No data	No data	LP	PK210879, PK210778
c.1296dup	p.Leu433Thrfs*9	FS dup	Truncating	4.07e-6	No data	No data	LP	UK6
c.1374G>A	p.Trp458*	Nonsense	Truncating	2.26e-5	No data	No data	LP	*M2194*
c.1501del	p.Val501*	Nonsense	Truncating	6.84e-7	No data	1× P	LP	2VR, 3K, PK210529
c.127T>G	p.Trp43Gly	Missense	NTrun	0	No data	No data	LP	890202
c.139A>C	p.Thr47Pro	Missense	NTrun	2.11e-5	[44]	1× P	LP	*M2257*, *M2258*
c.446T>G	p.Leu149Arg	Missense	NTrun	7.95e-6	No data	1× VUS	LP	PK170930
c.460G>A	p.Gly154Arg	Missense	NTrun	1.30e-5	No data	No data	VUS	690046

Table 2. Continued

cDNA Change	Protein Change	Type	Effect	GnomAD v4.1.0	First Publication	ClinVar	ACMG Designation	Pedigree
c.478+1G>A	p.His160?	Splice	Truncating	2.06e-4	[43]	No data	VUS	PK200728, PK210410, *M2187*, *M2188*, *M2189*, *M2190*, *M2191*, *M2193*, *M2196*, *M2203*, *M2204*, *M2206*, *M2207*, *M2208*, *M2212*, *M2213*, *M2214*, *M2215*, *M2217*, *M2219*, *M2220*, *M2224*, *M2228*, *M2231*
c.1237G>A	p.Gly413Arg	Missense	NTrun	6.57e-6	No data	No data	VUS	B-0829
ALG9								
c.119_131+17del	p.Glu40fs	FS del	Truncating	0	No data	No data	P	PK14053
c.131+2T>G	p.Glu44?	Splice	Truncating	8.54e-6	No data	No data	LP	M2249
c.184_185del	p.Phe62Glnfs*18	FS del	Truncating	0	No data	No data	LP	PK210648
c.309_328del	p.Trp103fs	FS del	Truncating	0	No data	No data	LP	M242
c.327T>G	p.Tyr109*	Nonsense	Truncating	0	No data	No data	P	PK14505
c.427C>T	p.Arg143*	Nonsense	Truncating	2.58e-6	No data	No data	P	P1496, LE1, M2255
c.521_524dup	p.Phe176Serfs*19	FS dup	Truncating	6.84e-7	No data	No data	P	PK210285
c.530T>A	p.Leu177*	Nonsense	Truncating	0	No data	No data	P	M1328
c.560C>A	p.Ser187*	Nonsense	Truncating	0	No data	No data	LP	M1868
c.565+1_565+5del	p.Ala188?	Splice	Truncating	0	No data	No data	LP	PK150065, PK210432
c.566_701del	p.Ala189fs	Large del	Truncating	0	No data	No data	LP	BE2
c.566-1G>A	p.Ala188?	Splice	Truncating	2.18e-5	No data	No data	P	Ox5211
c.681G>A	p.Trp227*	Nonsense	Truncating	6.57e-6	[21]	1× P	P	890,216
c.754_757del	p.Phe252Ilefs*4	FS del	Truncating	0	[45]	1× P	P	M2253
c.761G>A	p.Trp254*	Nonsense	Truncating	0	No data	No data	P	M884
c.896_1602del	p.Gly299fs	Large del	Truncating	0	No data	No data	P	M2047
c.1012_1018+8delinsATAC	p.Phe338fs	FS del	Truncating	0	No data	No data	LP	UK7
c.1018+1G>A	p.Val340?	Splice	Truncating	1.85e-5	No data	No data	LP	M2256
c.1071G>A	p.Trp357*	Nonsense	Truncating	1.86e-6	No data	No data	P	590116
c.1174_1602del	p.His392_Tyr534del	Large del	Truncating	0	No data	No data	P	BE1
c.1219C>T	p.Arg407*	Nonsense	Truncating	5.58e-6	No data	No data	P	M157, PK210512, *M2252*
c.1324+2T>C	p.Gly442?	Splice	Truncating	1.37e-6	No data	No data	LP	M2254
c.1363C>T	p.Arg455*	Nonsense	Truncating	1.36e-5	[45]	1× VUS	P	UK9
c.1441C>T	p.Arg481*	Nonsense	Truncating	1.37e-6	No data	No data	LP	M2243
c.1464del	p.Pro489Leufs*35	FS del	Truncating	0	No data	No data	LP	M2251
c.1472del	p.Asn491Ilefs*33	FS del	Truncating	1.08e-5	No data	No data	LP	UK8
c.1695G>A	p.Trp565*	Nonsense	Truncating	2.05e-6	No data	No data	P	M983
c.860A>G	p.Tyr287Cys	Missense	NTrun	7.13e-5	[46]	1× P	LP	M2260, M2259
c.1019-14_1019-5del	p.Val340?	Splice	NTrun	0	No data	No data	LP	PK3699, PK200564
c.334C>T	p.Arg112Cys	Missense	NTrun	1.05e-5	No data	1× VUS	VUS	M1256

ACMG, American College of Medical Genetics; FS del, frameshift deletion; LP, likely pathogenic; NTrun, nontruncating; P, pathogenic; VUS, variants of uncertain significance.
[a]c.1038+1G>T variant is most frequently found in the Finnish population.

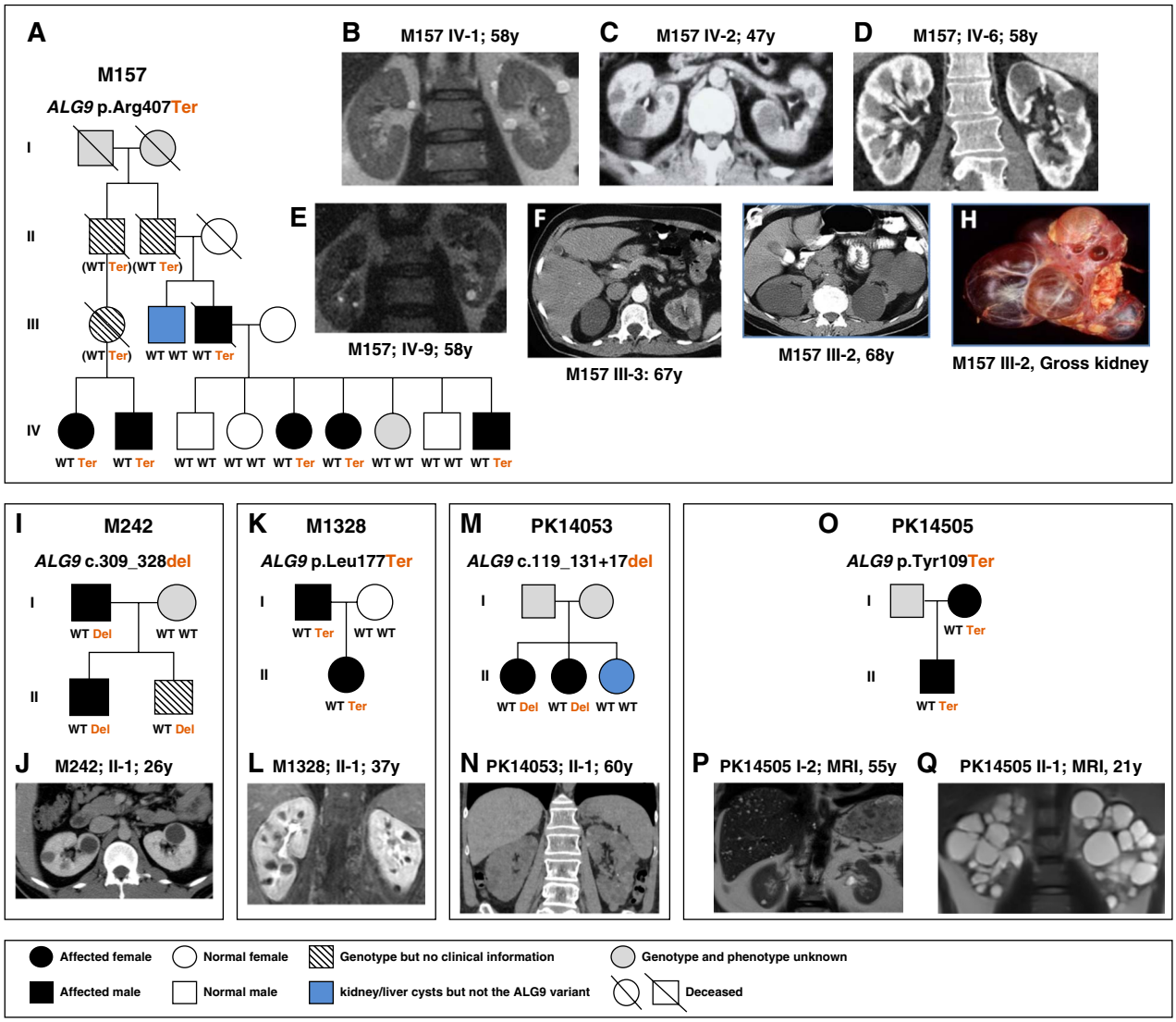

Figure 3. Pedigree and imaging details of five multiplex ALG9 families. (A) Pedigree M157: In a *PKD1* and *PKD2* unlinked family, six distantly related members in two generations had the *ALG9* nonsense variant p.Arg407*. (B–F) The phenotype was consistently a few kidney cysts and no or limited liver involvement. (G and H) Interestingly, III-2 had a few, large kidney cysts but not the *ALG9* variant; a genetic cause of the cysts has not been determined despite WGS. IV-7 also has approximately 20 liver and approximately eight kidney cysts but did not have the *ALG9* variant. DCM was found in some family members (Table 1) but did not segregate with the *ALG9* variant. (I) Pedigree M242: Three family members in two generations had the *ALG9* variant c.309_328del. (J) Bilateral cortical kidney cysts were seen in II-1 and I-1, and I-1 had numerous liver cysts. Clinical information was not available for II-2. (K) Pedigree M1328: The *ALG9* nonsense variant p.Leu177* was detected in II-1 and her father. (L) II-1 had a few bilateral kidney cysts and no liver cysts, while I-1 had a few small bilateral kidney cysts and one large liver cyst. (M) Pedigree PK14053: Two affected sisters had the ALG9 deletion, c.119_131+17del, and bilateral kidney cysts and no liver cysts. (N) II-1 had an enlarged left kidney and an eGFR=28 ml/min per 1.73 m^2 at age 66 years. II-3 had a few cysts but not the *ALG9* variant. Family history was uncertain. (O) Pedigree PK14505: The affected mother and son had the *ALG9* nonsense variant, p.Tyr109*. (P and Q) The son had severe kidney enlargement (MIC 1E) at age 21 years but normal kidney function, while the mother had normal kidney function and one cyst per kidney. The key indicates the significance of shading. Only affected individuals or others with genetic and/or clinical information available are shown. The type and age at imaging are shown. DCM, dilated cardiomyopathy; MIC, Mayo Imaging Class; WGS, whole-genome sequencing.

whether cysts were more common than expected by chance, we analyzed an age- and sex-matched MCBB control group, which showed a greater number of kidney and liver cysts in ALG8 individuals (Supplemental Figure 6). In addition, the median number of kidney and liver cysts was significantly higher in the ALG8 group (see Figure 5, B and C for details). Individuals with a common (gnomAD v4.1.0=0.02%) variant, c.478+1G>A, found at a weakly scoring splice donor site and found much more often in the MCBB (part 3; n=22) compared with the clinical population (part 1; n=1), was excluded from the analysis because of doubts over pathogenicity. Kidney cyst occurrence and number were much more frequent in individuals with other P/LP variants than

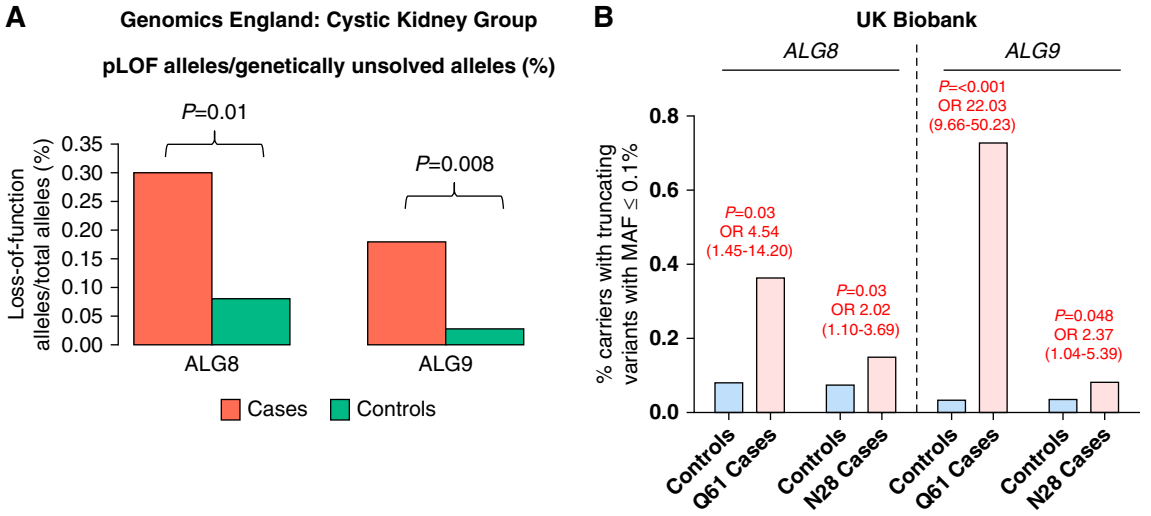

Figure 4. Analysis of individuals with *ALG8* and *ALG9* predicted loss-of-function variants in cystic kidney versus control populations. (A) Bar plots showing the percentage of predicted loss-of-function (pLOF) *ALG8* (left) and *ALG9* (right) alleles in the genetically unsolved 100kGP:PKD cohort population (total alleles=1660; red bars) versus a genetically unsolved and non-PKD control population (total alleles=49,506; green bars). For *ALG8*: there were five and 40 predicted loss-of-function variants in cases and controls, respectively, and for *ALG9*: three and 15 predicted loss-of-function variants in cases and controls, respectively. *P* values are calculated using chi-squared tests with Yates's correction. (B) Distribution of predicted loss-of-function variants with a gnomAD MAF ≤0.1% in Q61 (cystic kidney disease) and N28 (other disorders of kidney and ureter) cases and controls without these codes in the UKBB population shows an enrichment in cystic cases. For ALG8: Q61 cases=3/825 (0.36%) and controls=268/333,876 (0.08%); N28 cases=11/7425 (0.15%) and controls=237/322,208 (0.07%). For ALG9: Q61 cases=6/825 (0.7%) and controls=111/333,876 (0.03%); N28 cases=6/7425 (0.08%) and controls=110/322,208 (0.03%). MAF, minor allele frequency; OR, odds ratio.

those with c.478+1G>A (see Supplemental Figures 7 and 8, Supplemental Table 6 for details). EHR review of the ALG9 subset indicated that 9/10 had kidney cysts while 4/10 had liver cysts (Figure 5D). In a 1:2 matched case:-control analysis, the presence of kidney cysts was higher (but not significantly so) in the ALG9 cases compared with controls (90% versus 56%; $P = 0.10$; odds ratio [OR], 7.2 [95% confidence interval (CI), 0.83 to 87.51]) and similarly for cyst number (see Figure 5E for details). Furthermore, the presence of liver cysts was not significantly higher in ALG9 cases than controls (44% versus 22%; $P = 0.38$; OR, 2.8 [95% CI, 0.5804 to 14.39]), nor the median number of cysts (see Figure 5F for details).

Monoallelic ALG8 Phenotype

To determine if kidney function was reduced in ALG8 individuals, the eGFR for part 1 and MCBB patients (part 3) were plotted and found to be less severe than a Mayo PKD2 population (Figure 6A). In the clinical ALG8 population (part 1), most individuals had preserved kidney function, but 11 of 62 had an eGFR <50; other variants or comorbidities might be significant in some of these cases (Table 1 and Supplemental Tables 1 and 2). TKV on average was mildly enlarged but quite variable; an atypical MIC[35] was quite common—2A (indicating asymmetric or few segmental cysts) in four cases and 2B (characterized by parenchymal atrophy) in five cases (Figure 6B, Table 1, and Supplemental Table 2). In the part 1 population, the mean age at diagnosis was 42 years (SD ±17), and abdominal pain was the most common initial presentation (n=14), followed by incidental imaging (n=7). Hypertension was diagnosed in 44% of individuals (n=27), with an average age at onset of 52 years (SD ±15; Table 1 and Supplemental Table 2). Liver cysts were found in 65% (n=41) of ALG8 individuals, with quite severe polycystic liver disease (a total liver volume of >2L) found in ten individuals (six men and four women; Table 1, Supplemental Figure 1, and Supplemental Table 2), but only one individual underwent a liver resection. In the nonselected MCBB (part 3) ALG8 cohort (mean age 63.3 years), kidney function was in the normal range for all but 3/14 individuals younger than 70 years (one with a *PKHD1* LP variant), milder than the part 1 ALG8 group (Figure 6A), and not significantly different from the controls (Supplemental Figure 9A). TKV was not generally higher in the part 3 cohort (Figure 6, A and B), but 19 of 28 (68%) were diagnosed with hypertension.

Monoallelic ALG9 Phenotype

In the clinical (part 1) cohort, the mean age of diagnosis was 46 years (SD ±19) and 45% were hypertensive. A decline in eGFR (<60 ml/min per 1.73 m^2) was found in 10/33 (30%) ALG9 individuals, including two with kidney failure (Figure 6C). The mean TKV was also enlarged, but this was driven by five individuals with MIC C–E; one had MIC 2A (Figure 6D, Table 1, and Supplemental Table 3). Only nine individuals had one or more liver cyst, with two having a total liver volume >2L. Within the MCBB population (mean age 72 years; SD ±15), 2/3 younger than 70 years had an eGFR <60 ml/min per 1.73 m^2, but kidney function did not significantly differ from controls (Supplemental Figure 9B).

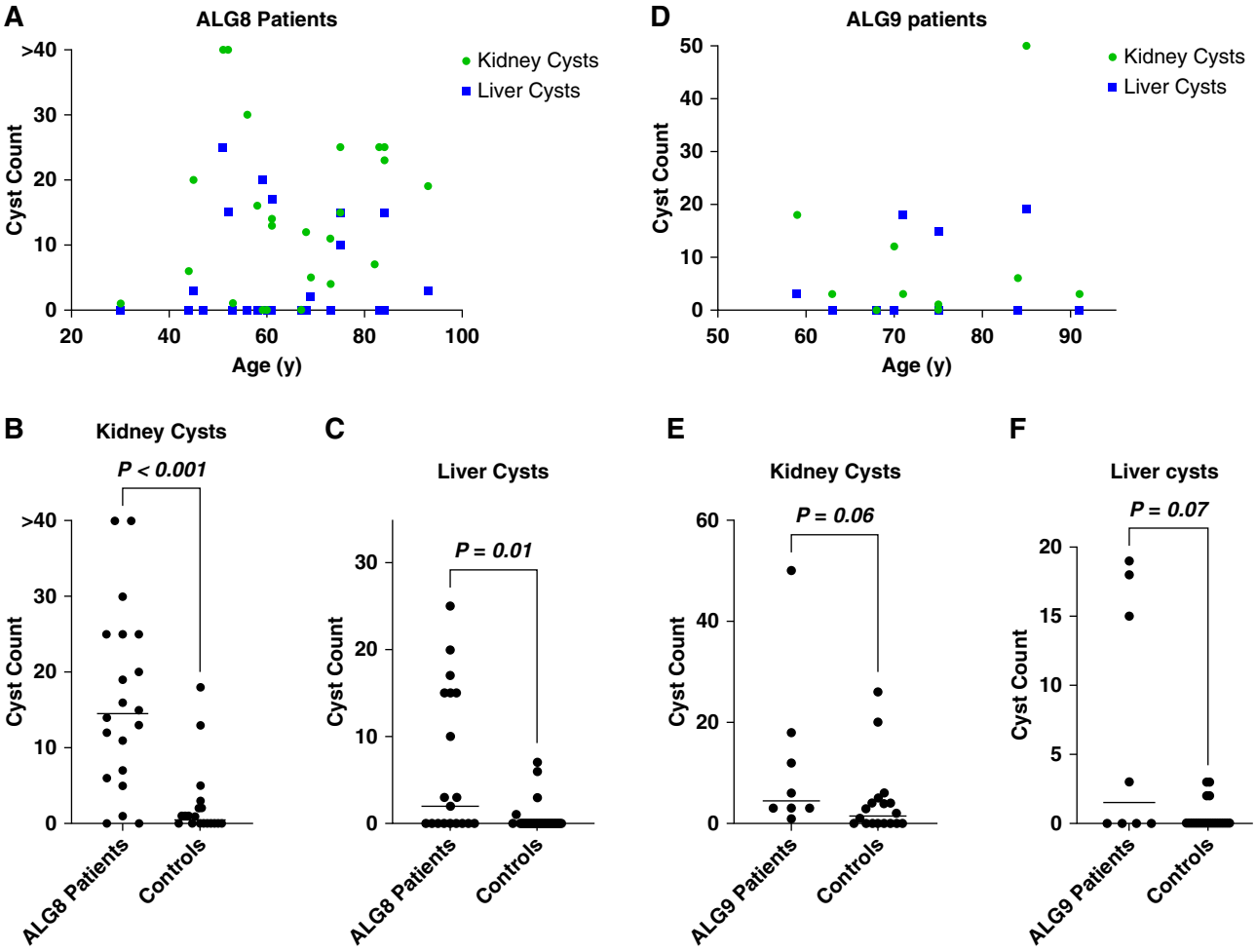

Figure 5. Analysis of kidney and liver cyst number in individuals with *ALG8* or *ALG9* P/LP variants in MCBB. (A) Plot of cysts in the kidney (green) and liver (blue) of ALG8 individuals relative to age. (B) Plot of number of kidney and (C) liver cysts found in ALG8 cases compared with an age- and sex-matched control population from MCBB. Kidney cyst number was significantly higher in the ALG8 group than controls (median cyst count of 14.5 in cases compared with 0.5 in controls, $P < 0.001$). (C) The median number of liver cysts was also significantly greater in ALG8 cases compared with controls (median cyst count of two in cases compared with zero in controls, $P = 0.01$). (D) Plot of cysts in the kidney (green) and liver (blue) of ALG9 individuals relative to age. (E) Plot of number of kidney and (F) liver cysts found in ALG9 cases compared with a 1:2 age- and sex-matched control population. (E) The median kidney cyst number was not statistically greater in the relatively small number of ALG9 cases compared with controls (4.5 compared with 1.5 in controls, $P = 0.06$). (F) The median liver cyst count was also not significantly greater in ALG9 cases (1.5 compared with zero in controls, $P = 0.07$).

Discussion

In this study, we provide strong evidence that monoallelic *ALG8* and *ALG9* P/LP variants can result in kidney and/or liver cysts. The level of individuals with *ALG8* pathogenic variants in the clinical population (51/3935, 1.3%) was significantly higher than that found in the gnomAD v3.1.2 database (95/76,000, 0.13%), with a P value of < 0.0001 and an OR of 10.49 (95% CI, 7.466 to 14.67). Likewise, the level of individuals with *ALG9* pathogenic variants in the clinical population (23/3935, 0.58%) was significantly higher than in gnomAD v3.1.2 (19/76,000, 0.03%), with a P value of < 0.0001 and an OR of 23.51 (95% CI, 13.16 to 43.71). Similarly, enrichment was seen in the 100kGP, UKBB, and MCBB PKD populations. Limited family data showed segregation of cyst development including in at least two generations for both genes, an important finding defining a monogenic disease. In the HALT PKD and TAME PKD clinical trial populations, with more rigorous definitions of ADPKD than in our cystic cohort, 0.1% and 0.3% had ALG8 or ALG9, respectively, compared with 80% PKD1 and 15% PKD2. In our clinical population, most of the individuals seemed to be sporadic, pointing to lower penetrance of cyst development for both loci. Consistent with this, most ALG8- or ALG9-positive individuals in the 100kGP, UKBB, and MCBB populations were not identified by ADPKD clinical codes. However, studies in the whole MCBB showed that most had some kidney cysts and 50% of ALG8 and 30% of ALG9 individuals had >10 kidney cysts, an indication of significant cystogenesis.[5,39] Therefore, these loci were enriched in cystic kidney populations, but multiple (or even single) kidney cysts were not always present. They are

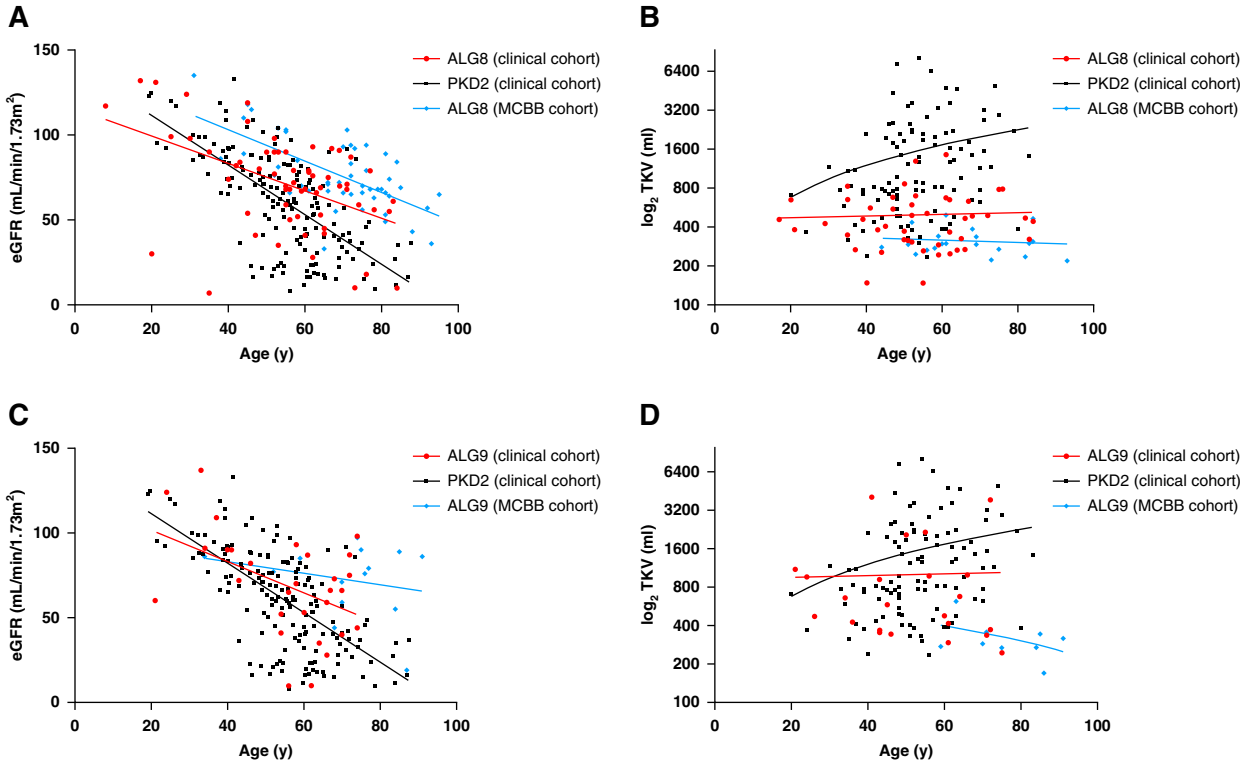

Figure 6. Analysis of eGFR and TKV in ALG8- and ALG9-affected individuals. (A) Plot of eGFR of ALG8 individuals in the clinical (part 1; red) and MCBB (part 3; blue) cohorts, and a Mayo Clinic PKD2 population (black), relative to age. The estimated slopes were −0.8061 (95% CI, −1.193 to −0.4192) for ALG8 part 1, −0.9211 (95% CI, −1.221 to −0.6213) for ALG8 MCBB, and −1.457 (95% CI, −1.710 to −1.205) for PKD2. Using an unpaired *t* test for two-group comparisons, the slopes of PKD2 and ALG8 part 1 differed significantly ($P < 0.001$), as did ALG8 part 1 and ALG8 MCBB ($P = <0.001$). (B) Plot of TKV on a log2 scale of ALG8 individuals in the clinical (part 1) and MCBB (part 3) cohorts, and the PKD2 control population, relative to age. The estimated slopes were 0.7218 (95% CI, −4.200 to 5.644) for ALG8 part 1, −0.6421 (95% CI, −3.457 to 2.173) for ALG8 MCBB, and 26.49 (95% CI, 2.824 to 50.15) for PKD2. The slopes of PKD2 and ALG8 part 1 differed significantly ($P < 0.001$), as did ALG8 part 1 and ALG8 MCBB ($P = 0.019$). (C) Plot of eGFR of ALG9 individuals in the clinical (part 1) and MCBB (part 3) cohorts, and the PKD2 control population, relative to age. The estimated slopes were −0.9213 (95% CI, −1.616 to −0.2272) for ALG9 part 1, −0.3400 (95% CI, −1.201 to 0.5206) for ALG9 MCBB, and −1.457 (95% CI, −1.710 to −1.205) for PKD2. The slopes of PKD2 and ALG9 part 1 differed significantly ($P < 0.001$), as did ALG9 part 1 versus ALG9 MCBB ($P < 0.001$). (D) Plot of TKV on a log2 scale of ALG9 individuals in the clinical (part 1) and MCBB (part 3) cohorts, and the PKD2 control population, relative to age. The estimated slopes were 1.578 (95% CI, −28.24 to 31.39) for ALG9 part 1, −4.754 (95% CI, −13.61 to 4.104) for ALG9 MCBB, and 26.49 (95% CI, 2.824 to 50.15) for PKD2. The slopes of PKD2 and ALG9 part 1 differed significantly ($P < 0.001$); however, the comparison between ALG9 part 1 and ALG9 MCBB did not show a significant difference ($P = 0.181$). CI, confidence interval; TKV, total kidney volume.

probably best described as ADPKD associated with lower penetrance (not all individuals developing cysts) and with variable expressivity (individuals having variable presentations in terms of cyst number).

Overall, the ALG8 kidney phenotype, because of the relatively small number of cysts, did not include significantly enlarged kidneys, with atypical MIC because of a few large cysts or atrophy quite common. Likewise, kidney function was usually in the normal range, findings consistent with other studies and indicating low penetrance in terms of clinically significant kidney disease.[20] However, a few individuals had greatly enlarged kidneys and/or lower eGFR (even occasionally kidney failure). In the smaller ALG9 population, the predominant phenotype was also relatively normal-sized kidneys, although one third had MIC 1C–1E, with a decline in kidney function/kidney failure more common than for ALG8, as previously described.[21]

For both ALG8 and ALG9, a few individuals with more severe disease had plausible *PKD1*, *PKHD1*, or other modifier variants. However, the reason for more severe disease was often unresolved. Pedigree M157, where the family member with the most prominent PKD did not have the familial *ALG9* variant, and PK14053 illustrated intrafamilial variability and genetic complexity associated with low-penetrance disorders. Genetic modifiers, along with other comorbidities, likely explained some of the disease variability, but larger populations will be needed to fully understand the variability. Digenic disease with a *PKD1* and an *ALG8* P/LP variant described in two families provided some support of *ALG8* as a modest enhancer of the PKD1 kidney phenotype.

Significant liver enlargement, usually with limited kidney cysts, was found in a minority of ALG8 cases, consistent with links to ADPLD, so ALG8 genic and other genetic (and nongenetic) modifiers are likely significant for

this complication.[27,30] Only one ALG8 individual required liver surgical intervention, and the overall phenotype was more akin to GANAB than PRKCSH or SEC63 and not displaying the female sex bias usually seen in ADPKD and ADPLD.[10] Liver cysts, and especially liver enlargement, were rare in ALG9.

As expected, the overall kidney phenotypes both in terms of the TKV and eGFR were more severe in the clinically selected population (part 1) compared with the genotypic one (part 3); only two ALG8 individuals (and zero ALG9) in the MCBB population were coded as ADPKD. The clinical ALG9 disease seemed more severe than ALG8, but this was not reflected in the TKV of the genotype-first cohort, although in a limited and older population, CKD3 or greater was seen in 5/10 ALG9 individuals. This suggests a possible fibrotic and a cystic component to ALG9, such as ALG5.[18] No ALG8 or ALG9 individuals in MCBB had severe polycystic liver disease, reflecting both the relative rareness of ADPLD and ALG8 as its cause. The normal population analysis provided a clearer view of the penetrance of ALG8 and ALG9 phenotypes; 50% and 30% had an ADPKD cyst number definition for ALG8 or ALG9, respectively. Related data for kidney function for the two genes showed approximately 10% and 50%–66% (limited data in older individuals), respectively, having CKD3 (no kidney failure was noted). It should be noted that penetrance data for other minor ADPKD/ADPLD genes are not yet available.

Given the enrichment of *ALG8* and *ALG9* P/LP alleles in cystic kidney, and *ALG8* in cystic liver, individuals, these genes should be included on screening panels for ADPKD/ADPLD. Despite the incomplete penetrance, finding of a pathogenic change should normally be considered significant in the patient with kidney and/or liver cysts if no other ADPKD gene variants are present. This diagnosis would generally indicate a low (ALG8) to moderate (ALG9) chance of eGFR reduction, with a small chance of significant polycystic liver disease for ALG8, and that treatment or enrollment in clinical trials for more typical ADPKD is probably not appropriate. Therefore, the risk of kidney failure in individuals with an ADPKD-*ALG8* or ADPKD-*ALG9* diagnosis should be considered very differently than for an ADPKD-*PKD1* patient, and nephrologists, genetic counselors, and insurance companies need to be aware of this difference. Because P/LP *ALG8* variants are quite common (approximately 0.1% of individuals), they likely account for a significant proportion of individuals with subclinical, multiple kidney or liver cysts identified from imaging studies.[7,27,40] Given the incomplete penetrance of ALG8 and ALG9, presymptomatic genetic diagnosis should be avoided in minors at familial risk.

In an individual with a severe ADPKD kidney phenotype, typical of the major loci, positive ALG8 or ALG9 findings should be treated with caution as the only cause of the disease. Other factors, such as missed P/LP variants in the major genes (especially the segmentally duplicated *PKD1*), should also be considered.[41] Conversely, interpretation of finding a P/LP *ALG8* or *ALG9* variant in an individual screened for a noncystic indication should be conservative. In such cases, recommending imaging of the kidney and liver would be appropriate, but labeling as ADPKD or ADPLD without support from imaging should be avoided. Finally, both biallelic variants of *ALG8* and *ALG9* are implicated in congenital disorders of glycosylation characterized by neonatal onset and a severe multiorgan phenotype.[42] In carriers of *ALG8* or *ALG9* pathogenic variants intending to conceive, the presence of a shared ancestor with their partner should be ascertained. The necessity of comprehensive *ALG8* or *ALG9* sequencing in the partner remains subject to debate and exhibits international variation in clinical practice.

Kidney cysts are seen as part of the pleiotropic phenotypes due to biallelic mutations at these loci, especially for ALG9, supporting a link between cysts and these genes.[28,29] A proposed mechanism of kidney and liver cyst development in monoallelic ALG8 and ALG9 is inefficient folding and trafficking of polycystin 1, due to defective glycosylation, as proposed for other ADPKD/ADPLD genes encoding endoplasmic reticulum–resident proteostasis components.[21,27] However, given the importance of this process for normal cellular function, the trafficking of other proteins is also likely affected. We screened for ADPKD extrarenal phenotypes and ones associated with the biallelic CDG due to ALG8 and ALG9 but did not find evidence of recurrent phenotypes. Although at this stage no clear other phenotypes beyond the kidney and liver have been associated with these monoallelic disorders, it will be important to collect information as the size of these recognized populations expands.

A strength of the study is the characterization of both a large clinical PKD/polycystic liver disease cohort, including multiplex families, and general population analyses. Limited phenotypic data are available for the 100kG and UKBB cohorts, but the MCBB allowed the phenotype associated with *ALG8* and *ALG9* P/LP variants to be explored. This MCBB cohort has an average age of approximately 61 years, often allowing analysis of phenotypic development over the individual's lifetime. However, the significant proportion of individuals older than 70 years, when simple kidney (and liver) cyst development becomes more common (and when there are limited data about normal average cyst number), complicated cyst number analysis in this older group.[5,39] However, overall, this study shows the value of population data to assess pathogenicity and penetrance of putative cystic loci.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/JSN/F62.

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Data Sharing Statement

All data are included in the manuscript and/or supporting information. Partial restrictions to the data and/or materials apply. Details of pathogenic variants and VUS in *ALG8* and *ALG9* is being deposited in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) with the patient diagnosis. For the UKBB, all the WES described in this paper are publicly available to registered researchers through the UKB data access protocol (https://www.ukbiobank.ac.uk/). Exomes can be found in the UKB showcase portal. Access to sequence data for the Genome England 100K Genome Project is described at https://www.genomicsengland.co.uk/initiatives/100000-genomes-project. The MCBB can be accessed through a collaboration with a Mayo researcher.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/JSN/F61.

Supplemental Methods
Supplemental Table 1. Details of other variants of interest.
Supplemental Table 2. Details of singleton patients with ALG8.
Supplemental Table 3. Details of singleton patients with ALG9.
Supplemental Table 4. Details of individuals with *ALG8* and *ALG9* pathogenic variants in the 100K genomes cystic kidney disease cohort.
Supplemental Table 5. Details of the MCBB patients with pathogenic *ALG8* and *ALG9* variants.
Supplemental Table 6. Details of carriers of *ALG8* c.478+1G>A variant.
Supplemental Figure 1. Imaging details of singleton ALG8 patients.
Supplemental Figure 2. Imaging details of singleton ALG9 patients.
Supplemental Figure 3. Abdominal CT images of digenic individuals with *ALG8* and *PKD1* pathogenic variants.
Supplemental Figure 4. Imaging details of MCBB ALG8 patients with a cystic phenotype.
Supplemental Figure 5. Imaging details of MCBB ALG9 patients with a cystic phenotype.
Supplemental Figure 6. Comparison of kidney and liver cyst number between ALG8 individuals versus controls in the MCBB cohort.
Supplemental Figure 7. Analysis of the ALG8 variant c.478+1G>A.
Supplemental Figure 8. Imaging details of carriers of ALG8 c.478+1G>A variant.
Supplemental Figure 9. Comparison of eGFR in ALG8 and ALG9 individuals in MCBB and matched MCBB controls.
Supplemental Acknowledgments

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