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

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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 8 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 100kGP (100kGP), UK Biobank (UKBB), 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 ~10x and ~24x greater than non-polycystic kidney disease (PKD) controls. Analysis of individuals with PKD phenotypes in 100kGP, UKBB, and MCBB identified 9 ALG8 (0.39%) and 9 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 (56%, >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 11/62 patients although surgical intervention was rare. The ALG9 kidney phenotype was also of mild cystic kidneys but enlarged livers were rare; for both genes chronic kidney disease 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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Key point #1: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and	Loss of function ALG8 and ALG9 variants were enriched in polycystic kidney/liver groups and ICD coded cystic individuals in population cohorts.

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Key point #2: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required."	The ALG8 and ALG9 kidney phenotype was usually mild to moderate, and lower eGFR or kidney failure were rare.
Key point #3: as follow-up to "Key Points: Please state the 2-3 key points of the article. The responses included here will be included with your final published paper. The key points should be complete statements and not duplications of your keywords or index terms. At least two key points are required."	ALG8 pathogenic variants sometimes resulted in severe polycystic liver disease.

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

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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 8 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 100kGP (100kGP), UK Biobank (UKBB), 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 ~10x and ~24x greater than non-polycystic kidney disease (PKD) controls. Analysis of individuals with PKD phenotypes in 100kGP, UKBB, and MCBB identified 9 ALG8 (0.39%) and 9 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 (56%, >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 11/62 patients although surgical intervention was rare. The ALG9 kidney phenotype was also of mild cystic kidneys but enlarged livers were rare; for both genes chronic kidney disease 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 are a group of inherited disorders that result in kidney cyst development and often kidney failure. The most common form is 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 ~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 US).[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 females.[3, 10] The related but much rarer autosomal dominant polycystic liver disease 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 ~78% and ~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 (y) compared to 74.8y for ADPKD-*PKD2*.[12] Allelic effects for *PKD1* (truncating or nontruncating pathogenic variants) are also associated with the age at kidney failure (55.1y and 65.8y, 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 autosomal dominant polycystic liver disease 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 ~75y due to fibrosis of non-enlarged 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 autosomal dominant polycystic liver disease.[19, 23, 27] Together these genes likely account for a few percent of total ADPKD families, 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], while 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 autosomal dominant polycystic liver disease populations compared to 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 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 ADPKD families, 6 had *ALG8* predicted loss-of-function variants, some with atypical cystic kidney disease.[31] A recent study described a large autosomal dominant polycystic liver disease (ADPLD)-*ALG8* family.[30] However, ALG8 family data is 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 ADPKD patients without *PKD1* or *PKD2* pathogenic variants that identified two with heterozygous *ALG9* LoF 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]; 7/11 (64%) with abdominal imaging had 5 or more kidney cysts. In a PKD gene panel screen of 100 German ADPKD patients one had a *ALG9* predicted loss-of-function variant.[33] Limited family data is available for ALG9 individuals, and the full extent of the phenotype/penetrance is unclear.

Here 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 (*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 Part 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 semi-automatically from the latest available CT 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 >2mm were recorded. Parapelvic cysts were excluded from the count. Estimated glomerular filtration rate (eGFR) was calculated from the most recent clinical serum creatinine measurements with the CKD-EPI 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 (below). The transcripts

employed for variant description were: *ALG8*, GenBank: NM_024079 and *ALG9,* GenBank: NM_024740. Frequency of variants are shown in the gnomAD v4.1.0 or v3.1.2 databases for the entire populations.

An unpaired t-test was employed for two-group comparisons, and the Mann–Whitney U test 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 χ2 tests with Yates' correction. Regression analysis was employed 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 employing a targeted NGS gene panel, or whole exome or whole genome sequencing (WES/WGS) 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.

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, Supplemental Table 1). A total of six

patients (33%) had eGFR <60mL/min/1.73m^2, including one patient with kidney failure at 73y (Table 1).

Singletons: In addition, 44 singletons with a clinically confirmed cystic phenotype and an *ALG8* P/LP variant were identified (Tables 2, Supplemental Table 2, and Supplemental Figure 1). The pathogenic variants were predicted loss-of-function in 42 individuals and missense in two. Two other individuals had *ALG8* missense variants classed as variants of uncertain significance (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 was not available (Supplemental Table 2). A total of 12 singleton patients (27%) had an eGFR <60mL/min/1.73m^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 = 10mL/min/1.73m^2 at 44y with both kidneys ~20cm in length, and some liver cysts (Supplemental Figure 3A,B). One brother had kidney failure at 48y, but genetic analysis of him or other family members was not possible. A second individual recruited from 100kGP:PKD cohort (UK6) had enlarged kidneys with multiple cysts but normal kidney function at 34y, 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 5 multiplex families including 14 affected individuals (see Figures 1, 3 and legend for details, Tables 1, 2). Three patients (21%) had an eGFR <60mL/min/1.73m^2, with none having kidney failure (Table 1).

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

Part 2: Analysis of cystic kidney individuals 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: WGS screening of 1486 individuals from a broadly selected cystic kidney and/or liver group (100kGP:PKD; see Supplemental Methods for details) and 28778 from an intellectual disability (control) cohort detected 6 (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 (Figure 1, Table 2, Supplemental Table 4). For *ALG9*, 3 (0.2%) probands were in the 100kGP:PKD and 14 (0.05%) in the control group (Figure 1, Table 2, 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 detail).

UK Biobank (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: MAF ≤ 0.1%) predicted loss-of-function variants showed the strongest association between Q61 and *ALG9* (0.7% among Q61 cases vs. 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 ADPKD patients identified within Mayo Clinic Biobank (MCBB): Using ADPKD ICD9 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] (Tables 2, 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=52786) ~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 (Table 2, Supplemental Table 5, Figure 1C, Supplemental Figures 4 and 5). Two ALG8 individuals had >40 kidney cysts and an ADPKD diagnosis (Part 2) and 14 had ≥10 cysts, including one with ICD9 code 753.10, but no kidney or liver cysts were detected in 2 patients (Figure 5A). To determine 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 6A,B). Also, the median number of kidney and liver cysts was significantly higher in the ALG8 group (see Figure 5B, C for details). Individuals with a common (gnomAD vs4 = 0.021%) 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 to 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 those with c.478+1G>A (see Supplemental Figures 7A-D and 8 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 were higher (but not significantly so) in the ALG9 cases compared to controls (90% vs 56%; *p*=0.10; OR=7.2 [95% CI: 0.83 to 87.51], and similarly for cyst number (see Figure 5E for details). Also, the presence of liver cysts was not significantly higher in ALG9 cases than controls (44% vs 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 11/62 had an eGFR <50; other variants or comorbidities might be significant in some of these cases (Tables 1, Supplemental Tables 1 and 2). TKV on average was mildly enlarged but quite variable; an atypical Mayo Imaging Class (MIC)[39] was quite common, 2A (indicating asymmetric or few segmental cysts) in 4 cases and 2B (characterized by parenchymal atrophy)

in 5 cases (Tables 1, Supplemental Table 2; Figure 6B). In the Part 1 population, the mean age at diagnosis was 42y (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 52y (sd±15; Tables 1, Supplemental Table 2). Liver cysts were found in 65% (n=41) ALG8 individuals, with quite severe polycystic liver disease (a total liver volume [TLV] of >2L) found in 10 individuals (6 males and 4 females) (Tables 1, Supplemental Table 2; Supplemental Figure 1), but only one individual underwent a liver resection. In the non-selected MCBB (Part 3) ALG8 cohort (mean age 63.3y), kidney function was in the normal range for all but 3/14 individuals <70y (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). Part 3 TKV was not generally higher (Figure 6A, B), but 19/28 (68%) were diagnosed with hypertension.

Monoallelic ALG9 phenotype

In the clinical (Part 1) cohort, the mean age of diagnosis was 46y (sd±19) and 45% were hypertensive. A decline in eGFR (<60 mL/min/1.73m^2) was found in 10/33 (30%) of ALG9 individuals, including two with kidney failure (Figure 6C). The mean TKV was also enlarged, but this was driven by 5 individuals with MIC C-E; 1 had MIC 2A (Table 1, Supplemental Table 3; Figure 6D). Only 9 individuals had 1 or more liver cyst, with 2 having a total liver volume >2L. Within the MCBB population (mean age 72y; sd±15), 2/3 <70y had an eGFR <60 mL/min/1.73m^2, but kidney function did not significantly differ from controls (Supplemental Figure 9B).

DISCUSSION

Here 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 (51/3,935, 1.3%) was significantly higher than found in the gnomAD v3.1.2 database (95/76,000, 0.13%), with a p-value of <0.0001 and an odds ratio (OR) of 10.49 (95% CI: 7.466–14.67). Likewise, the level of individuals with *ALG9* pathogenic variants in the clinical population (23/3,935, 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: 13.16–43.71). 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 and TAME 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 to 80% PKD1 and 15% PKD2. In our clinical population, most individuals appeared 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. But studies in the whole MCBB showed that most had some kidney cysts and 56% of ALG8 and 27% of ALG9 individuals had >10 kidney cysts, an indication of significant cystogenesis[5, 40]. Therefore, these loci were enriched in cystic kidney populations, but multiple (or even single) kidney cysts were not always present. They are 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, due to the relatively small number of cysts, did not include significantly enlarged kidneys, with atypical MIC due to 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 a 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 penetrant disorders. Genetic modifiers, along with other comorbidities, likely explained some of the disease variability, but larger populations will be needed to full 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 autosomal dominant polycystic liver disease, so ALG8 genic and other genetic (and non-genetic) modifiers are likely significant for this complication.[27, 30] Only one ALG8 individual required 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 autosomal dominant polycystic liver disease.[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 to 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 as well as a cystic component to ALG9, like ALG5.[18] No ALG8 or ALG9 individuals in MCBB had severe polycystic liver disease, reflecting both the relative rareness of autosomal dominant polycystic liver disease and ALG8 as its cause. The normal population analysis provided a clearer view of the penetrance of ALG8 and ALG9 phenotypes; 56% and 27% had an ADPKD cyst number definition for ALG8 or ALG9, respectively. Related data for kidney function for the two genes showed ~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/autosomal dominant polycystic liver disease genes is 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/autosomal dominant polycystic liver disease. Despite the incomplete penetrance, finding of a pathogenic change should normally be considered significant in the patient with kidney and/or liver cysts. 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 enrolment in clinical trials for more typical ADPKD probably not appropriate. Therefore, the risk for 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 counsellors, and insurance companies need to be aware of this difference. Since P/LP *ALG8* variants are quite common (~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, 41] Given the incomplete penetrance of ALG8 and ALG9, pre-symptomatic 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.[42] Conversely, interpretation of finding a P/LP *ALG8* or *ALG9* variant in an individual screened for a non-cystic indication should be conservative. In such cases, recommending imaging of the kidney and liver would be appropriate, but labelling as ADPKD or autosomal dominant polycystic liver disease without support from imaging should be avoided. Lastly, both biallelic variants of *ALG8* and *ALG9* are implicated in congenital disorders of glycosylation characterized by neonatal onset and a severe multiorgan phenotype.[43] 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 pleotropic 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/autosomal dominant polycystic liver disease 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 impacted. We screened for ADPKD extrarenal phenotypes and ones associated with the biallelic CDG associated with 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 is 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 ~61y, often allowing analysis of phenotypic development over the individual's lifetime. However, the significant proportion of individuals >70y, when "simple" kidney (and liver) cyst development becomes more common (and when there is limited data about normal average cyst number), complicated cyst number analysis in this older group.[5, 40] However overall, this study shows the value of population data to assess pathogenicity and penetrance of putative cystic loci.

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Table 1: Details of Families with *ALG8* or *ALG9* pathogenic variants

Demographics					Clinical details			Abdominal Imaging									Other details
Pedigree (study)	Pathogenic variant	Subject	Sex	Race	Dx, age (y)	eGFR, age (y)	HTN, age (y)	Type	Age (y)	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, 82y	CT	82	~35LK, ~15RK	215	254	469	2A	Nu	1624	2B	-
		II-2	F	W	AbP, 38	78, 61	Y, 59y	CT	61	BNu	398	276	674	1B	-	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	LKBl, 38	KF, 73	Y, 38y	CT	67	BNu	220	414	634	1A	-	1395	2G	CaG in Lu, AdCa, *PKD1* p.Asn1867Ser
		II-3	F	W	Screen, 59	66, 63	Y, 53y	CT	62	4EK	129	119	248	1A	Nu	1172	2H	ArCa
P907 (Oviedo)	c.705del (p.Phe235Leufs*13)	I-1	M	W	Screen	-	Y, 67y	-	-	BMS	-	-	-	-	-	-		Alz (73y), *NPHP1* p.Ser566?
		II-1	F	W	Screen	45, 65	Y, 65y	-	-	3LK, 5RK	-	-	-	-	MS	-	-	*NPHP1* p.Ser566?, *INVS* p.Glu903?
		II-4	F	W	Screen	50, 56	Y	US	-	2LK	-	-	-	-	-	-	-	*NPHP1* p.Ser566?
		II-5	F	W	LK At, 36	52, 58	Y, 27y	-	-	AtLK, MSRK	-	-	-	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, 1LgRK	355	138	493	2A	Nu Lg	1656	2K	-
		II-2	M	W	Inc, 33	76, 62	Y, 33y	MR	61	BMLgEx	568	884	1452	2A	Nu S	1860	2L	KCHe (57y),
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	>6 EK	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	BMS, 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-1	M	W	-	-	N	-	-	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**	**Subject**	**Sex**	**Race**	**Dx, age (y)**	**eGFR, age (y)**	**HTN, age (y)**	**Type**	**Age (y)**	**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	-	73, 68	N	CT	67	BM	-	-	-	-	1	-	3F	DCM
		IV-1	F	W	-	70, 58	-	MRI	57	BFEx	-	-	-	-	-	-	3B	-
		IV-2	M	W	Screen	65, 56	-	CT	47	BF	-	-	-	-	-	-	3C	-
		IV-5	F	W	Screen	66, 67	Y, <61y	US	61	7 B	-	-	-	-	-	-	-	-
		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, 52y	MRI	43	2LK, 2RK	167	198	365	1A	-	-	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	<70	-	-	US	70	BF	-	-	-	-	1 Lg	-	-	PNeph
		II-1	F	W	Nd	109, 37	N	MRI	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, NA	Y	MRI	55	1LK, 1RK	-	-	-	NA	M	-	3P	-
		II-1	M	W	HTN, NA	>60, 21	Y	MRI	21	BNu	491	606	1097	1E	-	-	3Q	TAV, *PKHD1* p.Met1fs

Dx age: age at diagnosis, HTN: hypertension, y: years.
Ab: abdominal, Ad: adrenal, AlbU: albuminuria, Alz: Alzheimer's, , At: atrophy, B: bilateral, BF: bilateral few, BM: bilateral multiple, BNu: bilateral numerous, Bl: bleeding, BrCa: breast cancer, CaG: calcified granuloma, Car: carotid, DCM: dilated cardiomyopathy, Dx: diagnosis reason, EK: each kidney, EctP: ectopic pregnancy, Ex: exophytic, F: few, Fl: flank, Hem: hemangioma, He: hemorrhage, HTN: hypertension, HyCa: hypercalcemia, Inc: incidental during imaging, KC: kidney cyst, Lg: large, LK: left kidney, Lu: lung, MS: multiple small, MIC: mayo Imaging Class, N: normal, NA: not applicable, Nd: never diagnosed, NL: nephrolithiasis, Nod: nodule, Nu: numerous, OvC: ovarian cysts, P: pain, PNeph, partial nephrectomy, Prt: proteinuria, Pul: pulmonary, Pyl: pyelonephritis, RK: right kidney, S: small, Screen: screening, Sco: scoliosis, TAV: tricuspid aortic valve, TLV: total liver volume, U: Unknown, W: White.

Table 2: Details of the *ALG8* or *ALG9* pathogenic variants

cDNA change	Protein Change	Type	Effect	GnomAD v4.0.0	First Publication	ClinVar	ACMG Designation	Pedigree
ALG8								
c.95+1G>A	p.Tyr32?	Splice	Truncating	3.85e-6	No data	2x LP	P	*M2226*
c.121C>T	p.Arg41*	Nonsense	Truncating	2.91e-5	No data	3x 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	[44]	2x LP	P	*M2202, M2221*
c.(369_546)del	p. Cys124Lysfs*23	Large del	Truncating	1.20e-6	No data	No data	LP	1P
c.478+1G>A	p.His160?	Splice	Truncating	2.06e-4	[44]	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.535C>T	p.Arg179*	Nonsense	Truncating	3.55e-5	[27]	2x 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	2x P	P	M2273, *M2197, M2227*
c.777+1G>A	p.Asn260?	Splice	Truncating	2.97e-6	No data	1x 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	[44]	1x P	P	M1792, *M2151, M2225*
c.1038+1G>T	p.Pro347?	Splice	Truncating	2.15e-4[a]	[27]	1x 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	[44]	9x P, 2x 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	1x 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	[45]	1x P	LP	*M2257, M2258*
c.446T>G	p.Leu149Arg	Missense	NTrun	7.95e-6	No data	1x VUS	LP	PK170930
c.460G>A	p.Gly154Arg	Missense	NTrun	1.30e-5	No data	No data	VUS	690046
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.Ala188f?	Splice	Truncating	2.18e-5	No data	No data	P	Ox5211
c.681G>A	p.Trp227*	Nonsense	Truncating	6.57e-6	[21]	1x P	P	890216
c.754_757del	p. Phe252Ilefs*4	FS del	Truncating	0	[46]	1x 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	[46]	1x 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.1019-14_1019-5del	p.Val340?	Splice	NTrun	0	No data	No data	LP	PK3699, PK200564
c.860A>G	p.Tyr287Cys	Missense	NTrun	7.13e-5	[47]	1x P	LP	M2260, M2259
c.334C>T	p.Arg112Cys	Missense	NTrun	1.05e-5	No data	1x VUS	VUS	M1256

[a] c.1038+1G>T variant is most frequently found in the Finnish population, ACMG: American College of Medical Genetics; FS del: frameshift deletion, IF del: inframe deletion, Spl: splice, Trun: truncating, NTrun: non-truncating; P: Pathogenic, LP: likely pathogenic, PM: Pathogenic moderate, VUS: Variants of uncertain significance.

Figure Legends

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 Mayo Clinic Biobank (MCBB) (**C**; Part 3). **A**: Part 1 included subjects from a range of clinical and observational studies (see Methods and Supplemental Methods for details) and sequenced at the 6 indicated sites (Total n=3935); the number of ALG8 and ALG9 families identified at each site and in total are indicated. ALG8 represented 1.30% 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), UK Biobank 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, 56% and 27% of ALG8 and ALG9 individuals had >10 kidney cysts.

Figure 1

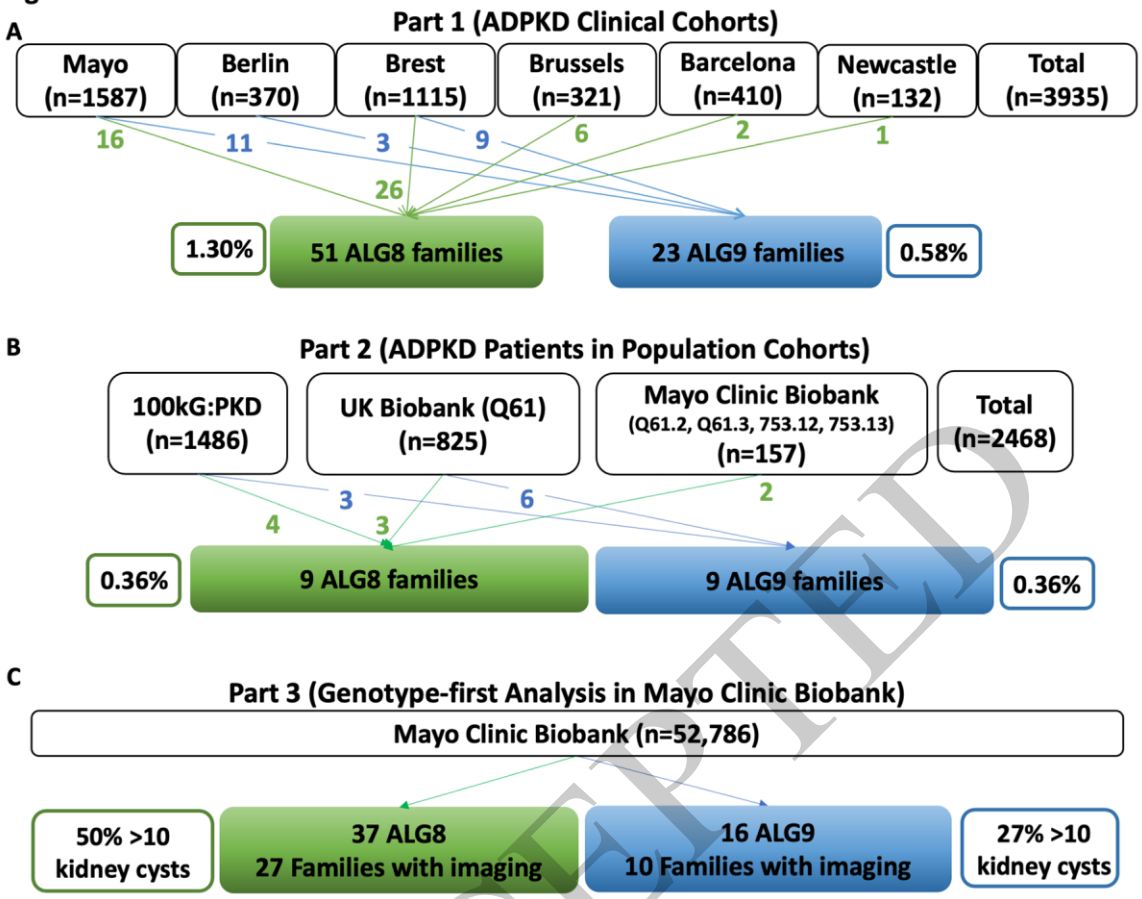


Figure 2. Pedigree and imaging details of seven multiplex ALG8 families: A-E, Pedigree M1021: Four individuals in two generations had bilateral kidney cysts, some predominating in the left kidney, all apart from II-2 had liver cysts, and all had the *ALG8* nonsense variant, p.Arg364*. Kidney function 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 73y. **H**: II-3 had just a few kidney and liver cysts, detected during donor evaluated, and normal kidney function. The father (I-1) had a diagnosis of PKD, and the sister (II-1) had a single cyst at 69y, 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*[48] and without a pathogenic variant in these genes[49], 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 40y identified 2 left kidney cysts. Two other LP recessive variants in the ciliopathy genes, *NPHP1* and *INVS*, were detected (Supplemental Table 3). **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 3 kidney and several large liver cysts, and the family history was uncertain. **M**, **O**, Pedigree 2VR: II-1 presented with abdominal pain at 20y and bilateral kidney cysts were detected on imaging, and an *ALG8* nonsense variant, p.Val501* 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**, **R**: II-1 presented with abdominal pain and PKD diagnosed on imaging at 18y, subsequently, I-1 was found to have kidney and liver

cysts. **S**, **T**, Pedigree PK200301: II-1 presented with hematuria at 12y, and cysts and the *ALG8* variant, p.Arg179*, were identified. The mother 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.

Figure 2

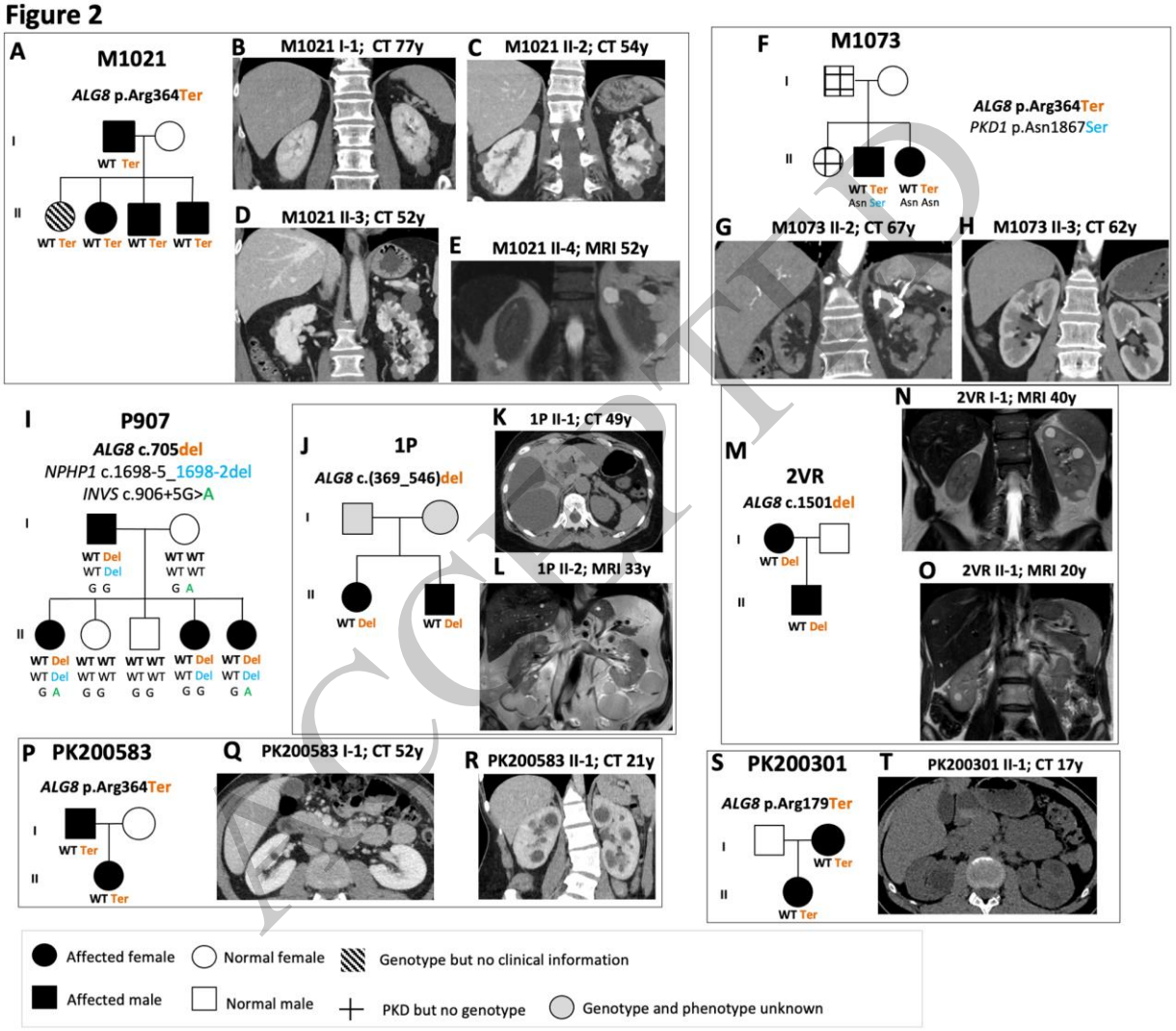


Figure 3. Pedigree and imaging details of five multiplex ALG9 families: A, Pedigree M157: In a *PKD1* and *PKD2* unlinked family, six distantly related members in two generations had the *ALG9* nonsense variant p.Arg407*. **B-F**: The phenotype was consistently a few kidney cysts and no or limited liver involvement. **G**, **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 ~20 liver and ~8 kidney cysts but did not have the *ALG9* variant. Dilated cardiomyopathy (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/1.73m^2 at 66y. 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, Q**: The son had severe kidney enlargement (MIC 1E) at 21y 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.

Figure 3

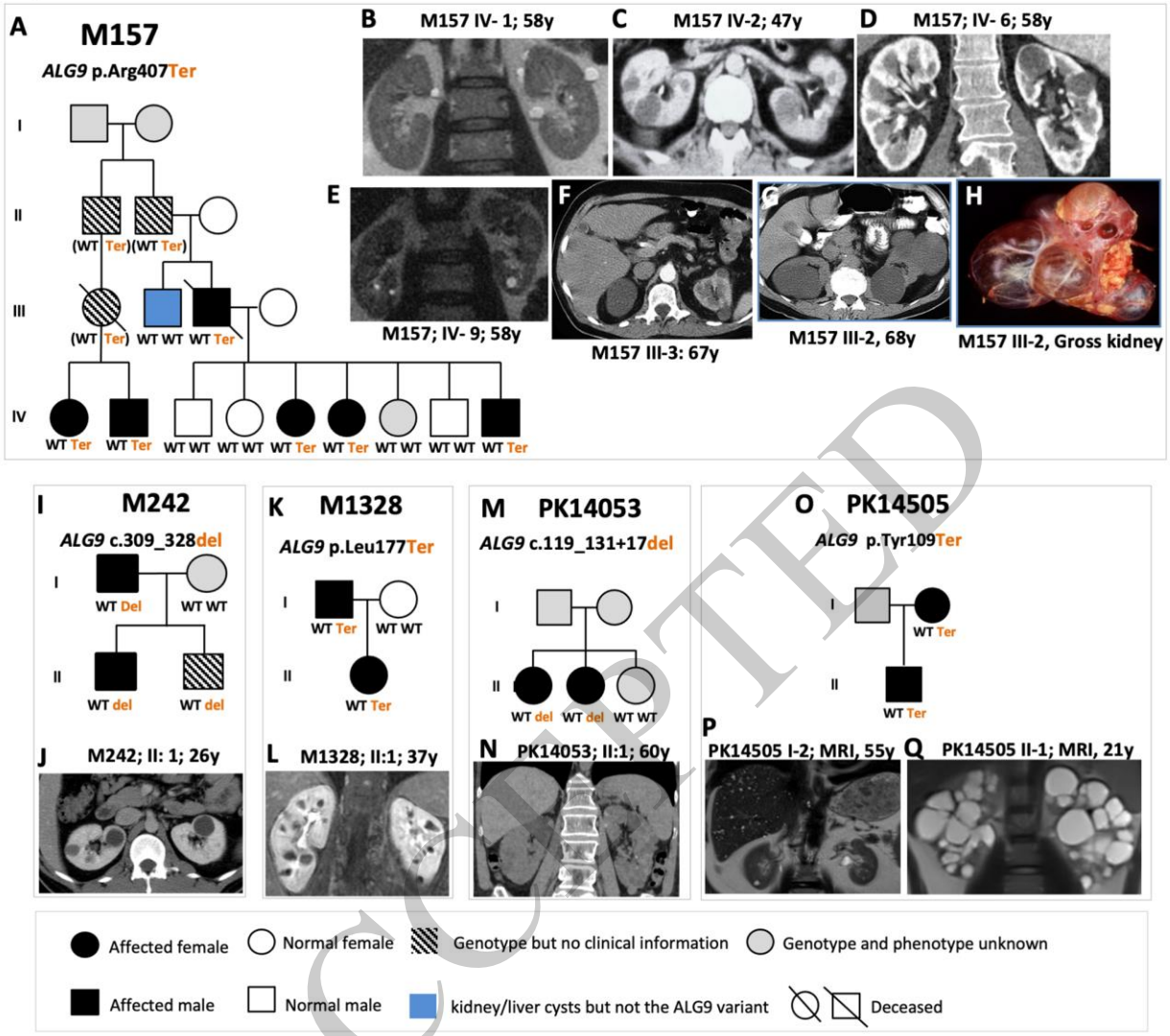


Figure 4. Analysis of individuals with *ALG8* and *ALG9* predicted loss of function variants in cystic kidney versus control populations. A: Bar plots showing the percentage of predicted loss-of-function *ALG8* (left) and *ALG9* (right) alleles in the genetically unsolved 100kGP:PKD cohort population (total alleles = 1660) red bars vs a genetically unsolved and non-PKD control population (total alleles = 49506) shown as green bars. For *ALG8*: there were 5 and 40 predicted loss-of-function variants in cases and controls, respectively, and for *ALG9*: 3 and 14 predicted loss-of-function variants in cases and controls, respectively. *p*-values are calculated using χ2 tests with Yates' 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 = 268/333876 (0.08%); N28 cases = 11/7425 (0.15%) and controls = 237/322208 (0.07%). For ALG9: Q61 cases = 6/825 (0.73%) and controls = 111/333876 (0,3%); N28 cases = 6/7425 (0.08%) and controls = 110/322208 (0.03%).

Figure 4

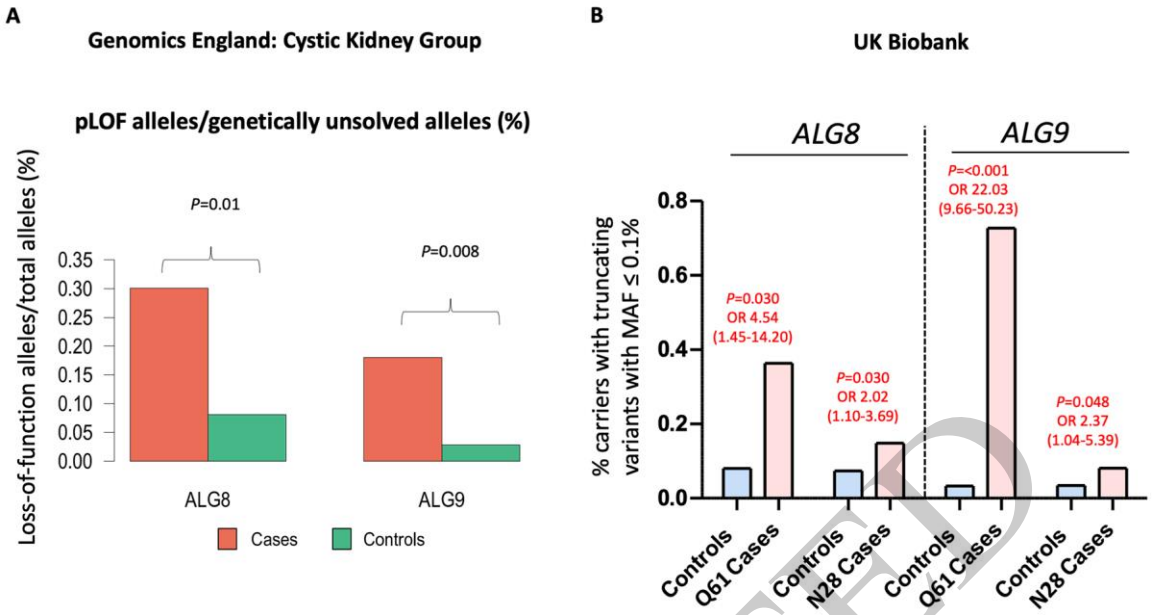


Figure 5. Analysis of kidney and liver cyst number in individuals with ALG8 or ALG9 P/LP variants in MCBB. A: Plot of cysts in the kidney (green) and the liver (blue) of ALG8 individuals relative to age. **B**: Plot of number of kidney and (**C**) liver cysts found in ALG8 cases compared to an age and sex matched control population from MCBB. **B**: Kidney cyst number was significantly higher in the ALG8 group than controls (median cyst count of 14.5 in cases compared to 0.5 in controls, p=0.002). **C**: The median number of liver cysts was also significantly greater in ALG8 cases compared to controls (median cyst count of 2 in cases compared to 0 in controls, p=0.01). **D**: Plot of cysts in the kidney (green) and the liver (blue) of ALG9 individuals relative to age. **E**: Plot of number of kidney and (**F**) liver cysts found in ALG9 cases compared to a 1:2 age and sex matched control population. **E**: The median kidney cyst number were not statistically greater in the ALG9 cases compared to controls (4.5 compared to 1.5 in controls, p=0.058). **F**: The median hepatic cyst count was also not significantly greater in ALG9 cases (1.5 compared to 0 in controls, p=0.065).

Figure 5

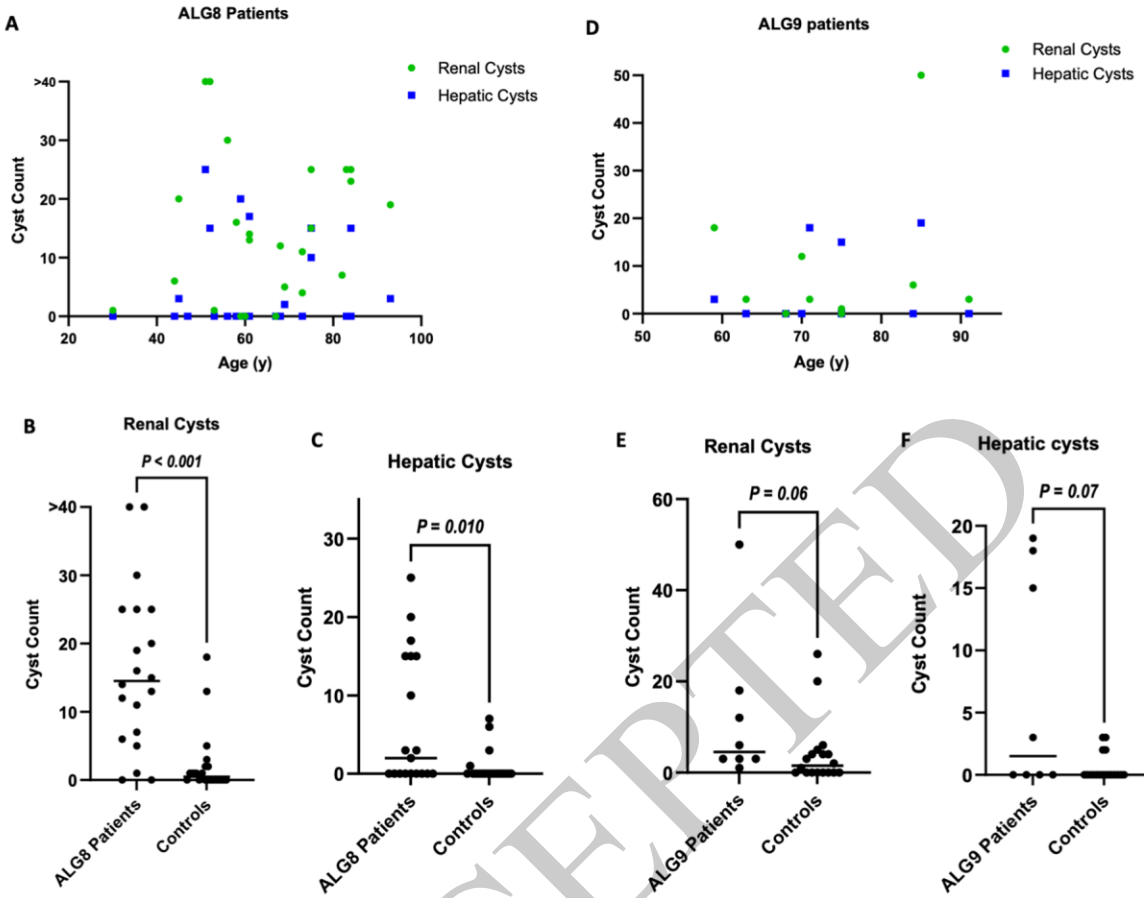
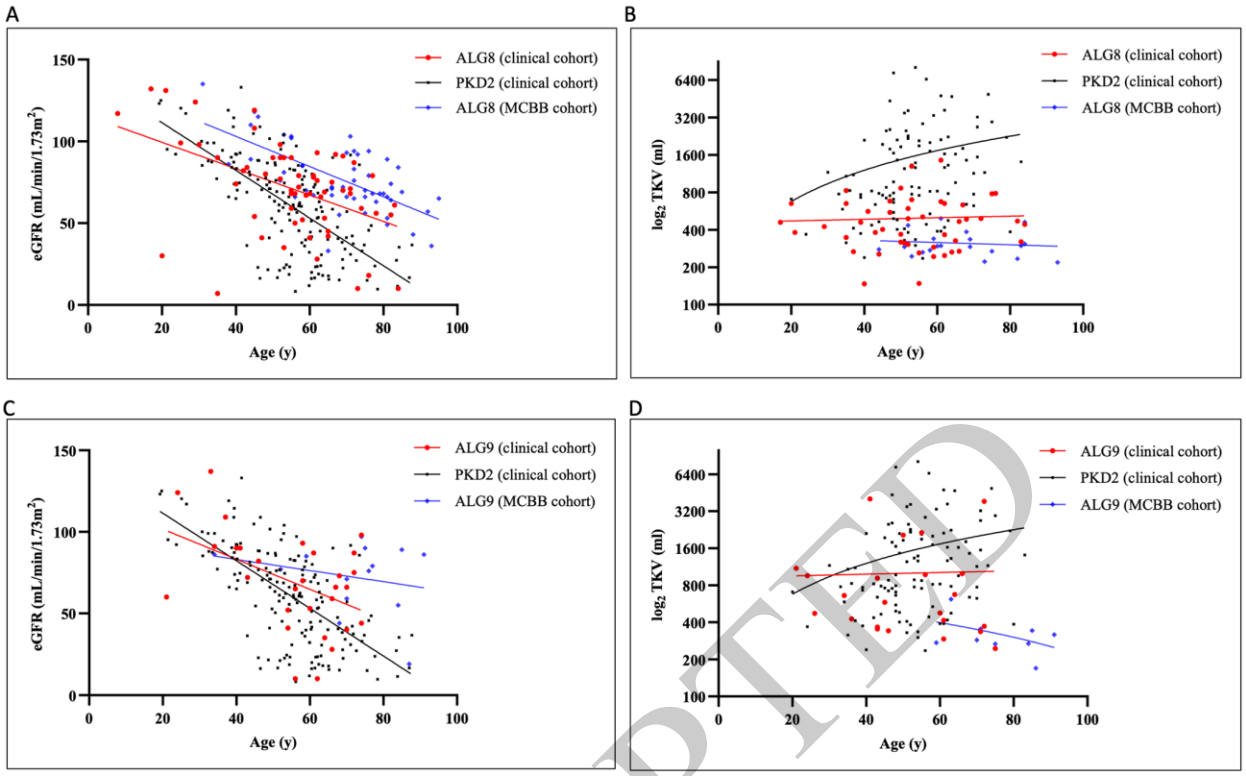


Figure 6. Analysis of eGFR and TKV in ALG8 and ALG9 affected individuals. A: Plot of eGFR of ALG8 individuals in the clinical (Part 1; red) and MCBB (Part 3; blue) cohorts, and a Mayo Clinic PKD2 population (black), relative to age. The estimated slopes were -0.8061 (95% CI: -1.193 to -0.4192) for ALG8 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 vs. ALG9 MCBB ($p < 0.001$). **D**: 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 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 ($p = 0.181$).

Figure 6



Cystic Phenotype Is Associated with Monoallelic *ALG8* and*ALG9* Pathogenic Variants

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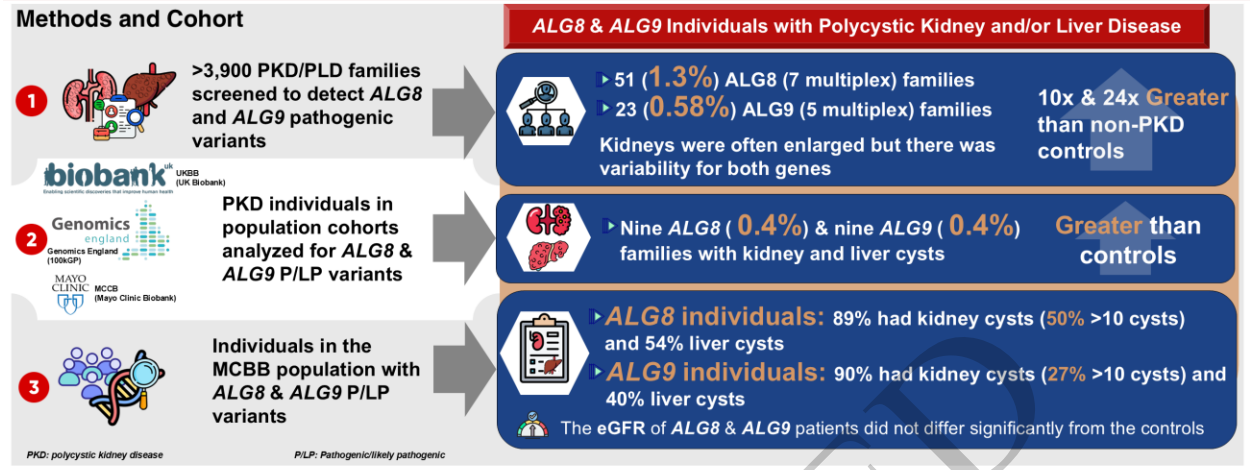

Conclusions: *ALG8* and *ALG9* are cystic kidney/liver genes with limited penetrance for lower eGFR.

Tabina Jawaid, Doua E. Barough, Sravanti Lavu, et al. ***Characterization of the Cystic Phenotype Associated with Monoallelic ALG8 and ALG9 Pathogenic Variants.*** JASN Doi: 10.1681/ASN.0000000613. **Visual Abstract by Hector M. Madariaga, MD, FASN**

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E. Ars reports the following:
Employer: Fundació Puigvert

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Elisabet Ars
Manuscript ID: JASN-2024-000977R2
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants.
Date of Completion: December 20, 2024
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M. Audrezet reports the following:
Employer: Molecular Genetic Unit

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Marie-Pierre Audrezet
Manuscript ID: JASN-2024-000977R3
Manuscript Title: Characterization of the Cystic Phenotype Associated with Monoallelic ALG8 and ALG9 Pathogenic Variants
Date of Completion: January 17, 2025
Disclosure Updated Date: May 21, 2024

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T. Baker reports the following:
Employer: Mayo Clinic

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Name: Tracy A. Baker
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 20, 2024
Disclosure Updated Date: November 20, 2024

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M. Barroso Gil has nothing to disclose.

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Name: Miguel Barroso Gil
Manuscript ID: JASN-2024-000977R3
Manuscript Title: Characterization of the Cystic Phenotype Associated with Monoallelic ALG8 and ALG9 Pathogenic Variants
Date of Completion: January 3, 2025
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J. Bublitz reports the following:
Employer: Mayo Clinic Rochester

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Name: Josh T. Bublitz
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
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Disclosure Updated Date: November 20, 2024

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G. Buia reports the following:
Employer: Centre Hospitalo-Universitaire de Brest

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Name: Guillaume Buia
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Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
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F. Chebib reports the following:
Employer: Mayo Clinic; Research Funding: Research grant- Otsuka pharmaceuticals; Natera; Regulus; Patents or Royalties: Patent no US20200368191A1; and Advisory or Leadership Role: PKD foundation- Chair of Education Advisory Panel; Center of Excellence Advisory panel; Board of Directors; Advisory board- Vertex, Otsuka.

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Name: Fouad T. Chebib
Manuscript ID: Disclosure Form for JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 19, 2024
Disclosure Updated Date: May 24, 2024

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E. Cornec-Le Gall reports the following:
Employer: Faculté de médecine de Brest; Centre Hospitalier Universitaire de Brest; Consultancy: Vertex, GSK, Rhythm Pharmaceuticals; and Advisory or Leadership Role: ERA-EDTA Genes&Kidney Working Group.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Emilie Cornec-Le Gall
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
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Disclosure Updated Date: December 2, 2024

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E. Coto has nothing to disclose.

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Name: Eliecer Coto
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
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Disclosure Updated Date: November 30, 2024

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K. Dahan reports the following:
Employer: Universite Catholique de Louvain; Institut de Pathologie et de Génétique de Gosselies; Consultancy: CHIESI, AstraZeneca, Alnylam; and Advisory or Leadership Role: President and member of advisory committes for 3 nonprofit patient organisations : AIRG, FAPA and Retina; Board of Directors of IPG.

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Name: Karin Dahan
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Title "Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
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Disclosure Updated Date: January 9, 2025

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N. Dahl reports the following:
Employer: Mayo Clinic; Consultancy: Otsuka Pharmaceuticals; Research Funding: I am a PI for clinical trials sponsored by Reata, Vertex and Regulus.; Honoraria: Otsuka Pharmaceutical, Natera; Advisory or Leadership Role: PKD Foundation; Natera Scientific Advisory Board; Speakers Bureau: I was on the unbranded speakers bureau for Otsuka until 12/2022; and Other Interests or Relationships: Medical Advisory Board, NKF NE Chapter (until 2023); Associate Editor, Kidney360.

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Name: Neera K. Dahl
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 19, 2024
Disclosure Updated Date: May 3, 2024

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N. Demoulin reports the following:
Employer: Cliniques universitaires Saint Luc; and Consultancy: CSL Vifor, Bayer.

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Name: Nathalie Demoulin
Manuscript ID: JASN-2024-000977R3
Manuscript Title: Characterization of the Cystic Phenotype Associated with Monoallelic ALG8 and ALG9 Pathogenic Variants.
Date of Completion: January 1, 2025
Disclosure Updated Date: November 21, 2024

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D. Elbarougy reports the following:
Employer: Mayo clinic

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Name: Doaa E. Elbarougy
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
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V. Gillion has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Valentine Gillion
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants,"
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Disclosure Updated Date: November 20, 2024

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B. Gitomer has nothing to disclose.

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Name: Berenice Y. Gitomer
Manuscript ID: JASN-2024-000977R2
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants,
Date of Completion: December 19, 2024
Disclosure Updated Date: May 2, 2024

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As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

A. Gregory reports the following:
Employer: Mayo Clinic

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Adriana Gregory
Manuscript ID: JASN-2024-000977R2
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants.
Date of Completion: December 19, 2024
Disclosure Updated Date: May 14, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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J. Halbritter reports the following:
Employer: Charité Universitätsmedizin Berlin; and Advisory or Leadership Role: Editorial Board Kidney International and Clinical Kidney Journal and Journal of Rare Diseases.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Jan Halbritter
Manuscript ID: Disclosure Form for JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 19, 2024
Disclosure Updated Date: June 11, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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P. Harris reports the following:
Employer: Mayo Clinic; Consultancy: Vertex, Mitobridge, Regulus, Otsuka, Janssen, Maze Therapeutics, CorrectorBio, Sen Therapeutics; Research Funding: Espervita, Navitor, Acceleron, Jemincare, Regulus; and Patents or Royalties: Bayer, Sanofi, Vertex, Mitobridge, Maze Therapeutics, Calico Life Sciences.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Peter C. Harris
Manuscript ID: JASN-2024-000977
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 11, 2024
Disclosure Updated Date: May 8, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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M. Hogan reports the following:
Employer: Mayo Clinic; Consultancy: Otsuka pharmaceuticals; Research Funding: Camurus, Regulus Pharmaceuticals., Reata.; Advisory or Leadership Role: Mayo Clinic Proceedings Quality & Outcomes Journal; No payment; Camurus Pharmaceuticals.; No payment; Sail Bio, No payment.; Glaxo-Smith-Kline, No payment. American Society of Nephrology, no payment. Regulus - no payment. Glaxo Smith Kline no payment.; and Other Interests or Relationships: PKD Foundation;; PKD Disease Outcomes Consortium; American Society of Nephrology;.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Marie C. Hogan
Manuscript ID: JASN-2024-000977R1,
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 11, 2024
Disclosure Updated Date: December 11, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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T. Jawaid has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Tabinda Jawaid
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants,
Date of Completion: December 3, 2024
Disclosure Updated Date: December 1, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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G. Joli reports the following:
Employer: Doctors Without Borders

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Giancarlo Joli
Manuscript ID: JASN-2024-000977R3
Manuscript Title: Characterization of the Cystic Phenotype Associated with Monoallelic ALG8 and ALG9 Pathogenic Variants,
Date of Completion: January 9, 2025
Disclosure Updated Date: January 9, 2025

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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F. Jouret reports the following:
Employer: University of Liege Academic Hospital (ULiege CHU); Consultancy: AstraZeneca; Bayer; Fresenius; Menarini; Vifor Pharma; and Advisory or Leadership Role: Belgian Society of Nephrology; French-speaking Society of Nephrology-Dialysis-Transplantation.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Francois Jouret
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 20, 2024
Disclosure Updated Date: November 20, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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T. Kline reports the following:
Employer: Mayo Clinic; Consultancy: Regulus Therapeutics, Inc.; Vertex Pharmaceuticals, Inc.; GlaxoSmithKline ; PYC Therapeutics; Research Funding: Regulus Therapeutics, Inc.; and Patents or Royalties: Disclosure at Mayo Clinic that is currently licensed by Regulus.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Timothy L. Kline
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 1, 2024
Disclosure Updated Date: July 24, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

As per ASN journal policy, I have disclosed any financial relationships or commitments I have held in the past 36 months as included below. I have listed my Current Employer below to indicate there is a relationship requiring disclosure. If no relationship exists, my Current Employer is not listed.

N. Larson reports the following:
Employer: Mayo Clinic; Research Funding: Sanofi; and Other Interests or Relationships: Genentech.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Nicholas B. Larson
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 20, 2024
Disclosure Updated Date: June 20, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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CJASN Clinical Journal of the American Society of Nephrology

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S. Lavu reports the following:
Employer: University of Texas MD Anderson Cancer Center

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sravanthi Lavu
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 11, 2024
Disclosure Updated Date: December 11, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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J. Ma has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Jun Ma
Manuscript ID: JASN-2024-000977R2
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 19, 2024
Disclosure Updated Date: May 21, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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C. Madsen reports the following:
Employer: Mayo Clinic

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Charles D. Madsen
Manuscript ID: JASN-2024-000977R1
Manuscript Title: "Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants."
Date of Completion: November 20, 2024
Disclosure Updated Date: May 16, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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S. McDonnell reports the following:
Employer: Mayo Clinic

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Shannon K. McDonnell
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 20, 2024
Disclosure Updated Date: November 20, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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ASN Journal Disclosure Form

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R. Neatu reports the following:
Employer: Newcastle University

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Ruxandra Neatu
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 22, 2024
Disclosure Updated Date: November 22, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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E. Olinger reports the following:
Employer: Saint Luc Academic Hospital

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Eric Gregory Olinger
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 21, 2024
Disclosure Updated Date: November 21, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
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J. Olson reports the following:
Research Funding: Exact Sciences, Inc

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Janet Elaine Olson
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 11, 2024
Disclosure Updated Date: December 11, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
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S. Orr has nothing to disclose.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sarah E Orr
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 30, 2024
Disclosure Updated Date: November 30, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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R. Perrone reports the following:
Employer: Tufts Medical Center; Consultancy: Otsuka, Janssen, Calico/AbbVie, Retex, Regulus, Vertex; Research Funding: Reata; Honoraria: Protalix; and Other Interests or Relationships: Section editor Renal Cystic Diseases UpToDate; PKD Foundation; Co-director PKD Outcomes Consortium Critical Path Institute; Co-Chair, Patient Registry Advisory Committee, PKD Foundation.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Ronald D. Perrone
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 21, 2024
Disclosure Updated Date: November 8, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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D. Peters reports the following:
Employer: Leiden University Medical Center; Consultancy: Mironid Ltd, BioCity Scotland ; Innoser; Torque Bio; Astrazeneca, Crown BioScience; Bayer; Patents or Royalties: Innoser; Crown BioScience; Bayer; and Advisory or Leadership Role: Mironid Ltd, BioCity Scotland; Torque Bio; Astrazeneca; Innoser.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Dorien J.M. Peters
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 21, 2024
Disclosure Updated Date: October 2, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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J. Sayer reports the following:
Employer: Newcastle University; Research Funding: Sanofi; and Honoraria: Genzyme, Sanofi.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: John Andrew Sayer
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: November 20, 2024
Disclosure Updated Date: August 15, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

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R. Schauer reports the following:
Employer: Mayo Clinic

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Rachel S. Schauer
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 1, 2024
Disclosure Updated Date: May 21, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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S. Senum reports the following:
Employer: Mayo Clinic

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Sarah R. Senum
Manuscript ID: JASN-2024-000977R2
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 19, 2024
Disclosure Updated Date: June 11, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

ASN Journal Disclosure Form

Date 01/14/2025

Author Theodore Steinman

Manuscript ID JASN-2024-000977R3

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

Disclosure Statements

I declare no conflicts of interests.

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
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ASN Journal Disclosure Form

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V. Torres reports the following:
Employer: Mayo Clinic; Research Funding: Mironid, Tribune Therapeutics, Palladio Biosciences, GSK, Sanofi, Reata, Regulus [all payments to Mayo Foundation for Preclinical and clinical trials and preclinical research]; Honoraria: Up to Date; Patents or Royalties: Consulting agreement with uResearch Technology and MFMER for imaging analytics for PCKD.; Repurposing of probenecid to treat PCKD.; System and method of classifying ADPKD; and Advisory or Leadership Role: International Society of Nephrology (Kaplan award committee), American Society of Nephrology (editorial board), PKD Foundation advisory board.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Vicente E. Torres
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants
Date of Completion: December 2, 2024
Disclosure Updated Date: December 2, 2024

ASN American Society of Nephrology
JASN Journal of the American Society of Nephrology
KIDNEY360 Accessing Our World From Every Angle
CJASN Clinical Journal of the American Society of Nephrology

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T. Watnick reports the following:
Employer: The University of Maryland School of Medicine; Research Funding: Co site PI for the Falcon Study (reata pharmaceutical)-this study has been terminated; Co site PI for a clinical trial funded by Regulus. The terms are governed by a research contract.; Honoraria: I recorded a video on the genetics of PKD for medscape and there was an honorarium. I don't know if this is a continuing education activity so will disclose.; Patents or Royalties: PKD DNA testing AThena Diagnostics; royalties, but both my spouse and I have declined these; I receive royalties from Uptodate for a chapter on polycystic kidney disease.; Advisory or Leadership Role: Scientific Advisory Committee for the Polycystic Kidney Disease Foundation registry and centers of excellence program; and Other Interests or Relationships: I serve on advisory committees for the PKD Foundation.

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Terry J. Watnick
Manuscript ID: JASN-2024-000977R1
Manuscript Title: Characterization of the cystic phenotype associated with monoallelic ALG8 and ALG9 pathogenic variants,
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H. Yang reports the following:
Employer: Mayo Clinic

I understand that the information above will be published within the journal article, if accepted, and that failure to comply and/or to accurately and completely report the potential financial conflicts of interest could lead to the following: 1) Prior to publication, article rejection, or 2) Post-publication, sanctions ranging from, but not limited to, issuing a correction, reporting the inaccurate information to the authors' institution, banning authors from submitting work to ASN journals for varying lengths of time, and/or retraction of the published work.

Name: Hana Yang
Manuscript ID: JASN-2024-000977R
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