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Familial Kidney Disease Phenocopying Hypertensive Nephropathy

Fezile Ozdemir[a, b] D. Deren Oygar[c] Ahmet Behlul[c] Salahi Ataç[c] Simge Bardak[c] Meral Yükseliş[c] Gregory Papagregoriou[d] Apostolos Malatras[d] Daniel P. Gale[e] Guy H. Neild[e] Constantinos Deltas[d, f] Cemal Gurkan[a, b]

[a]Fazıl Küçük Faculty of Medicine, Eastern Mediterranean University, Famagusta, Cyprus; [b]Turkish Cypriot DNA Laboratory, Committee on Missing Persons in Cyprus Turkish Cypriot Member Office, Nicosia, Cyprus; [c]Nephrology Department, Nicosia State Hospital, Burhan Nalbantoglu General Hospital, Nicosia, Cyprus; [d]School of Medicine, University of Cyprus, Nicosia, Cyprus; [e]UCL Centre for Nephrology, University College, London, UK; [f]Biobank.cy Center of Excellence in Biobanking and Biomedical Research, University of Cyprus, Nicosia, Cyprus

Keywords
Alport syndrome · Autosomal dominant · COL4A4 · Tubulointerstitial disease · Hypertensive nephropathy

Abstract
Introduction: Familial kidney disease is common in Cyprus and previous studies have found that the majority of families have mutations in Alport syndrome genes COL4A3/4/5. We have collected data from over 50 Turkish Cypriot families in whom kidney disease appears to follow an autosomal dominant pattern, and looked for pathological variants in these genes. ***Methods:*** Probands from 55 families underwent massive parallel DNA sequencing using a glomerular gene panel for familial hematuria, and whole-exome sequencing (WES) was also performed in 22 of them. Clinical records were reviewed. ***Results:*** Likely pathogenic variants were identified in 7 of the 55 families (COL4A3 [3], COL4A4 [2], and COL4A5 [2]), leaving 48 unsolved families. Among the latter a common missense variant of uncertain significance (COL4A4:p.G545A), was present in 5 families (9.1%). In contrast to families with a pathogenic variant in COL4A3/4 and a clear glomerular phenotype the 5 families (54 patients with clinical and genetic data), manifested near dominant susceptibility with incomplete penetrance, presenting with hypertension, variable and intermittent microscopic hematuria, and minimal proteinuria, <1 g/day until the estimated glomerular filtration rate (eGFR) fell below 30 mL/min, after which it increased in some individuals. Of those over age 50, 20% had reached end-stage by median age of 66 (48–80) years. ***Conclusions:*** We describe a kidney disease with mild hypertension that is more characteristic of a tubulointerstitial disease and phenocopies hypertensive nephropathy. While the variant COL4A4:p.G545A is not responsible for a Mendelian CKD phenotype, it appears to increases the susceptibility, acting as a hypomorphic variant contributing to Alport spectrum nephropathy. Early detection and treatment with ACE inhibitors should prolong kidney survival to an age where hemodialysis is avoided.

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Correspondence to:
Guy H. Neild, g.neild@ucl.ac.uk

Introduction

The Eastern Mediterranean has the highest incidence of kidney failure, as reported to the European Renal Association (ERA-EDTA) by Greece, Israel, and Greek Cypriots [1]. We have previously reported a high incidence of renal failure and familial kidney disease in northern Cyprus among Turkish Cypriots, where the incidence was 2–3 times greater than that reported in northwestern Europe by the UK, Norway, Finland, and Denmark [2].

Our investigation of Greek Cypriots with familial kidney disease has shown that the majority of patients have either hematuric nephropathy, often accompanied by significant proteinuria (termed here the "glomerular phenotype"), associated with heterozygosity for pathogenic rare variants within the *COL4A3*, *COL4A4*, or *CFHR5* genes [3–6], or a tubulointerstitial phenotype (that is, CKD in the absence of hematuria or glomerular proteinuria) typically associated with pathogenic rare variants in the *PKD1*, *PKD2*, *MUC1*, or *UMOD* genes [7]. We investigated 55 Turkish Cypriot families with evidence of CKD in at least two generations in whom we suspected pathogenic variants in *COL4A3* and *COL4A4*.

Methods

Study Population

Cyprus is the third largest island in the Mediterranean inhabited by a majority of Greek Cypriot population, with the largest minority (approximately 18%) Turkish Cypriot. Genetic studies indicate that Greek and Turkish Cypriots have similar origins with close affinities to southeastern Anatolia and the Near East [8–10]. Turkish Cypriots are currently centered on the northern part of Cyprus. A 2006 census of the Turkish Cypriot population revealed that of 178,031 de jure citizens, 120,007 were born to parents who were both born in Cyprus [11].

Families

The study was conducted at Dr. Burhan Nalbantoglu Nicosia State Hospital in northern Cyprus, a multispecialty tertiary care hospital that provides renal services to all of northern Cyprus. Family trees were created for families with 2 or more members with evidence of CKD [12] (shown in Figure 1a–e). Families were contacted and were either visited in their villages or at the hospital. The requirement for the use of family names (surnames) was introduced only in 1974. Families of 10 children were common until the 1970s.

DNA Isolation and PCR-RFLP

DNA extractions were carried out using the PureLinkTM Genomic DNA Mini Kit (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's procedure. All DNA samples were quantified using a Qubit 2.0 fluorometer (Invitrogen, Thermo Fisher Scientific) and a Qubit dsDNA HS Assay Kit (Invitrogen, Carlsbad, CA, USA).

The index patients from a total of 55 families underwent NGS, which included parallel analysis of a 5-gene panel containing *COL4A3, COL4A4, COL4A5, CFHR5,* and *FN1* as previously described [6]. Twenty-two patients had previously undergone whole-exome sequencing (WES). WES analysis was performed as we previously described [13]. See Supplementary material (for all online suppl. material, see https://doi.org/10.1159/000546094) for PCR methodology (and online suppl. Fig. S1).

Clinical Investigations

The upper limit of normal for creatinine in men was 97 μmol/L, for women 80 μmol/L, and for blood urea nitrogen 7.1 mmol/L. Kidney function (eGFR) was reported by the MDRD formula.

Proteinuria was initially measured by 24-h urine collection, and a normal status was defined as a protein concentration <140 mg/day and an albumin concentration <30 mg/day. More recently, proteinuria has also been measured as the protein and albumin/creatinine ratio (Uacr <30 mg/mg and Upcr <200 mg/mg).

Hematuria was investigated historically by urine microscopy and more recently by urine dipstick tests. Hematuria was deemed positive and equivalent to "a trace" on a dipstick if there were 3–4 red blood cells per high-power field.

Kidney biopsies were performed in two families. Biopsy specimens were routinely examined by light microscopy and immunofluorescence, and in 1 case electron microscopy data were available.

CKD staging as shown in the family trees (Fig. 1a–e: stage 0, no evidence of kidney disease; stage 1, eGFR>90 and microscopic hematuria; stage 2, eGFR 60–89 mL/min, microscopic hematuria, and/or Uacr >30 mg/mg; stage 3, eGFR in the range of 59–30 mL/min; stage 4, eGFR 29–15; and stage 5, kidney failure. The diagnostic criteria were based on KDIGO guidelines [12].

Study Groups Investigated

After we observed the *COL4A4* p.G545A variant in our sequencing results, we tested 54 members of our 5 families. We also tested at least 1 member from 85 families with some evidence of a glomerular phenotype

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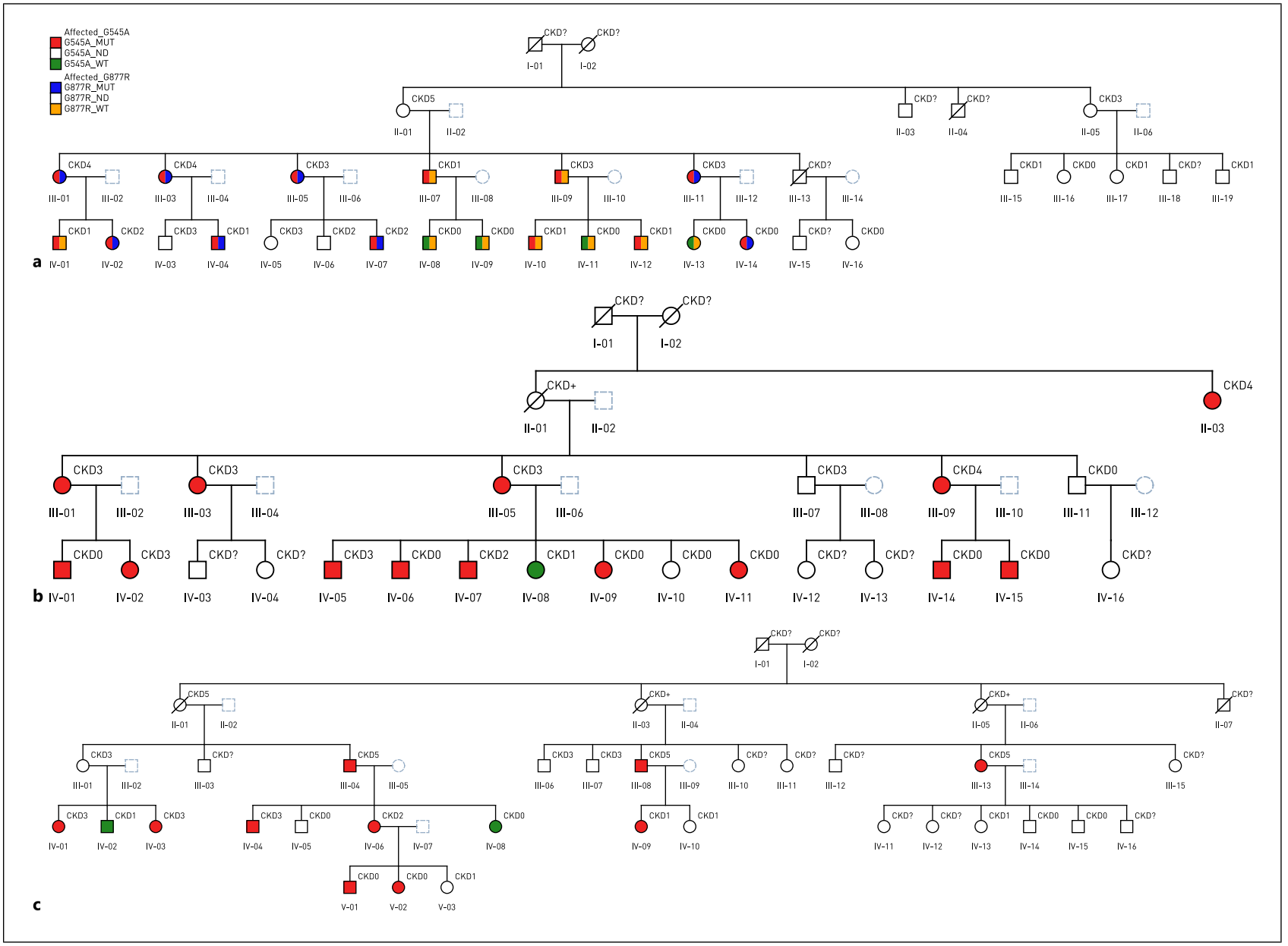

(Figure continued on next page.)

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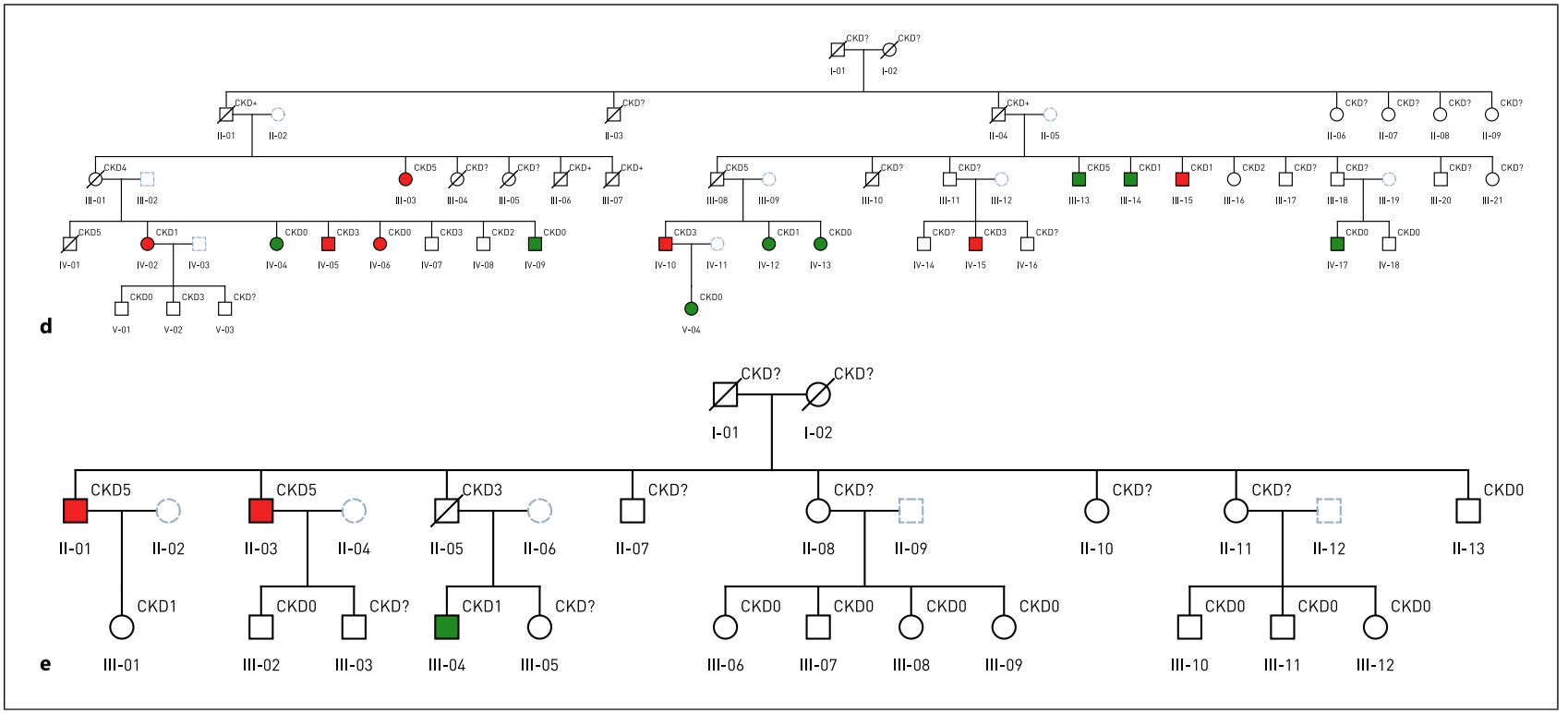

Fig. 1. a–e Five family pedigrees showing cosegregation with p.G545A. Symbols: squares are males, and circles are females. Red fill have the p.G545A mutation; green is for the normal gene (wild type), and clear is "no PCR performed." CKD stages 1–5 shown as superscript. CKD 0 means information available but no evidence of CKD. CKD ? means no information available. CKD+ means known to have CKD but no clinical information extant. Diagonal line through symbol means premature death. Family 1(a) also shows cosegregation with the p.G877R variant. Red fill or red half-fill indicates the G545A mutation, green indicates the normal gene (wild type), and clear is "no PCR performed". The G877R mutation is shown in blue half-filled symbols; the wild type is shown in yellow.

Table 1. Analysis of observed cosegregation

Family	Number of individuals with available clinical and molecular results (excluding those positive for the p.G877R variant)	Number of individuals positive heterozygous for the p.G545A variant	Number of individuals with CKD stages 1–5, concordant to positivity for the p.G545A variant	Number of individuals with CKD stages 1–5 discordant to positivity for the p.G545A variant	Probability of *N* or more concordant under null
1A	9	5	9	0	0.00195
1B	15	14	8	7	0.49
1C	12	10	9	3	0.073
1D	15	7	11	4	0.0592
1E	3	2	2	1	0.5
Total	54	38	39	15	0.000748

Binomial probability of observed cosegregation under the null hypothesis of random transmission of COL4A4:p.G545A at each informative meiosis was calculated using the binomial cumulative distribution function, and a single affected founder was assumed for each pedigree. Combined $p = 0.000748$.

Table 2. Clinical information from family members shown on five family trees

Family	Family members, *N*	All clinically affected (CKD stages 1–5)[a], *N* (variant present)[e]	Clinically unaffected (CKD stage 0), *N* (variant present)	No clinical Info[b], *N*	Age at first CKD[c], stage 3/KRT	Affected and age >50-year KRT (%)[d]
1 (a)	24[f]	12 (5/5)	7 (0/4)	5	60/65	1/11 (9)
1 (b)	24	11 (8/9)	8 (6/6)	5	63/0	0/7
1 (c)	33	18 (8/9)	6 (2/3)	9	67/67	4/14 (29)
1 (d)	44	20 (6/9)	8 (1/6)	16	61/60	3/15 (20)
1 (e)	20	5 (2/3)	9 (0)	6	57/61	1/4 (25)

Family trees – see Fig. 1a–e. [a]Clinically affected: evidence of renal disease (stages 1–5), including all reported cases of "kidney disease" but no survival data. [b]No clinical information: no information available because of death or diaspora. [c]Median age at CKD stage 3/kidney replacement therapy (KRT). [d]Affected and aged >50 years. KRT%: percentage who received KRT after the age of 50 years. [e]Variant present (x/y): y is the number of family members tested for *COL4A4* p.G545A, and x is the number showing the heterozygous mutation G545A. [f]Family 1 a) – members with variant G877R are excluded from these data.

(at least 1 person with hematuria or proteinuria) for p.G545A. Twelve families (14%) had a member with this variant. As controls, we examined a total of 172 unrelated healthy volunteers.

Statistical Analysis

Genotype and allele frequencies for both p.G545A and the wild type were calculated via the genotype counting method. The observed and expected genotype frequencies for both alleles were compared according to the Hardy-Weinberg equilibrium by using controls and the chi-square test (2-tailed test). Comparison of allele frequency in the replication cohort was compared to that among healthy controls using Fisher's exact test (two-tailed).

Results

Genetic Investigation of Members of Five Families (n = 54)

Likely pathogenic variants in *COL4A3/4/5* were identified in 7 of the 55 families initially investigated (*COL4A3* (3), *COL4A4* (2), and *COL4A5* (2)), leaving 48

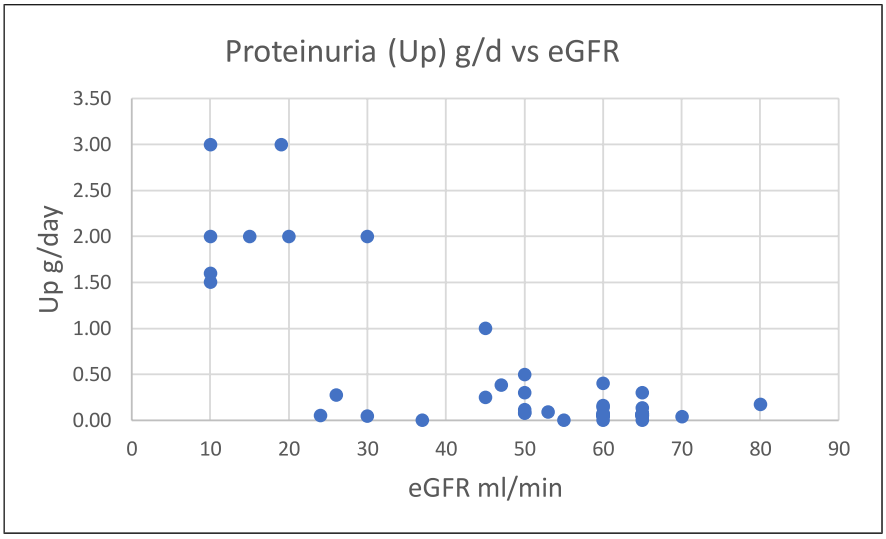

Fig. 2. Proteinuria (Up) g/day versus estimated glomerular filtration rate (eGFR). eGFR (mL/min) versus maximum (Up) g/d in 46 patients in our 5 families.

unsolved families. *COL4A4*:p.G545A was found in 5 of 55 families investigated by DNA sequencing (9.1%). Subsequently, we examined a replication set of 85 families with evidence of familial kidney disease most likely with a glomerular phenotype (at least 1 person with hematuria or proteinuria) and found 12 families (14%) with the p.G545A variant.

In one of the 5 families, we also found a pathogenic variant *COL4A3*:p.G877R (family 1a). Excluding those patients carrying the variant p.G877R, we investigated 54 available members from these 5 families for the p.G545A variant, and the minor allele frequency was 35% ($\chi^2 = 10$, $p = 0.001$).

Affected individuals were assigned to CKD stages 1–5. We found that the variant p.G545A cosegregated with kidney disease more frequently than expected based on random transmission (p value = 0.000748, Table 1). As controls, a total of 172 unrelated healthy volunteers, with a mean age of 56 years were investigated for the p.G545A variant, which was present in 4 (2.3%) of individuals in this cohort, similar to the gnomAD allele frequency. Hardy Weinberg Equilibrium χ^2 was 0.07 ($p = 0.78$). COL4A4:p.G545A was therefore, significantly enriched among the families in the validation cohort compared with healthy individuals from the Turkish Cypriot population ($p = 0.0005$).

Clinical Phenotype of Family Members (n = *66)*

In the 5 families, 66 members were affected with CKD stages 1–5; a further 38 were unaffected (CKD 0); and no information available in 41 members. The clinical data from these 5 families are summarized in Table 2 and by family trees (shown in Fig. 1a–e). Genetic and clinical data are available from 54 members.

Of the affected members: mildly raised blood pressure was universal and was easily controlled with 1–2 drugs. There was no case of accelerated hypertension considered relevant to deteriorating kidney function. Hematuria could be intermittent or absent. Among the 46 people whose urine was tested on one or more occasions, 34 had a positive result at least once (74%). We found that the proteinuria test was 0–1+ according to a dipstick test until the eGFR was less than 30 mL/min. Proteinuria versus eGFR is shown in Figure 2, documenting the observation that proteinuria was not greater than 1 g/d until the eGFR was less than 30 mL/min. We noted that for proteinuria (more than 140 mg/d) in patients with an eGFR >50 mL/min, approximately 50% of the urine protein was albumin, and this percentage increased to 80–90% when the proteinuria exceeded 2.0 g/d with eGFR values less than 30 mL/min.

The age of onset of CKD and ESKD in the 5 families is shown in Table 2. The median age of the 38 patients with a GFR <60 mL/min at first detection was 61 years (range 34–84). Among family members with clinical evidence of renal disease and aged older than 50 years, 19.6% had progressed to ESKD at a median age of 66 years (range 48–80 years).

Histology was performed for 2 families and revealed tubulointerstitial disease with interstitial fibrosis, tubular atrophy and extensive global glomerular sclerosis, with some glomeruli exhibiting segmental sclerosis. On one of the biopsies, electron microscopy was performed and showed patchy thinning of the glomerular basement membrane measured at 159 nm (a value less than 260 nm

is diagnostic for thin glomerular basement membranes). In one family, a 52-year-old female developed nephrotic syndrome, and a renal biopsy showed membranous nephropathy (see Fig. 1. C, IV-01). She is now in remission following a course of immunosuppression. Her data are not included in Table 2.

In Cyprus, diabetes mellitus is very common, and we have not specifically evaluated this topic in these families. The data recorded show that of the 65 family members over the age of 50 years with clinical information available, 40% with no renal disease (stage 0) had diabetes, and 40% with stage 1–5 disease were diabetic. Neither hearing loss nor eye problems were reported as a familial trait in any family studied, and screening for these traits was not performed.

Digenic Family

In one of the five families (shown in Fig. 1a), DNA sequencing identified a second novel variant, COL4A3: p.G877R (c.2629G>A) that is classified as likely pathogenic strong by Varsome. CKD stages 3–4 were present in 4 patients with both variants, and CKD stage 3 was present once in a patient with only the p.G545A variant. In the latter case, there was no proteinuria despite an eGFR of 50 mL/min. In the former, all had proteinuria, but the maximum was 1.2 g/day with an eGFR of 20 mL/min.

Discussion

While investigating families with autosomal dominant (AD) kidney disease presumed to be owing to mutations in *COL4A3/4/5* genes (Alport spectrum nephropathy), we found that a subset of families had a clinical presentation that was characteristic of hypertensive nephropathy [14, 15]. This was first noted when we reviewed our original 55 samples that had undergone NGS for COL4A3/4/5 and found 5 families with the common variant COL4A:p.G545A, who all had this clinical phenotype.

The large number of people affected in these 5 families has allowed us to perform a detailed analysis of the natural history of this kidney disease, which is indolent and asymptomatic until the disease is advanced and it constitutes an important cause of ESKD, usually in the seventh decade of life.

Among the initial 5 families investigated with 66 members with clinical evidence of renal disease, we observed the following: mild hypertension, little or no proteinuria until the eGFR <30 mL/min (shown in Fig. 2), variable microscopic hematuria, and kidney failure occurred in 20% of those affected who are aged >50 years.

These families often fulfilled the clinical KDIGO criteria for AD tubulointerstitial disease, which include CKD with bland urinary sediment, no to moderate proteinuria, and normal or small kidney size on ultrasound, with their pedigree consisting of at least 2 affected family members in 2 successive generations [16]. Histology revealed tubulointerstitial disease with interstitial fibrosis and tubular atrophy and extensive global glomerular sclerosis [17]. One of the family members had a renal biopsy which included electron microscopy that showed areas of thin glomerular basement membrane typical for Alport syndrome (see family 1 (e), Figure 1).

In the past 20 years, there have been an increasing number of reports of AD kidney failure associated with heterozygous pathogenic variants of *COL4A3* or *COL4A4* [4, 18–22]. Although initially considered to be a benign condition (benign familial hematuria), end-stage renal failure was first reported in elderly individuals with these variants in 1985 [23].

Both AD and X-linked Alport syndrome have recently been reported as causes of AD tubulointerstitial disease [24, 25], and several mild pathogenic variants in the *COL4A5* gene are associated with a much attenuated form of Alport syndrome with late-onset kidney failure [26]. These variants have widened the spectrum of Alport syndrome nephropathy to include a hypertensive nephropathy phenotype.

We subsequently studied a total of 85 families and observed significant enrichment in the frequency of COL4A4:p.G545A, as at least 1 patient in 12 families had this variant (14%). In the 5 families that we concentrated our study here, it is evident that the variant segregated with the disease substantially more frequently than it would be expected by chance (see Table 1).

It is a common variant and in gnomAD v4.0, which is a register of whole-genome sequencing data, the variant is most commonly found in people from the "Middle East," with an allele frequency of 0.082. We note the allele frequency of 2.3% observed in our control cohort is lower than the data from GnomAD cohort, possibly reflecting the fact that individuals with hematuria or other evidence of kidney disease were excluded from the former but not the latter.

In silico variant predictions suggest that COL4A4: p.G545A is pathogenic based on the use of Polyphen as a "probably damaging," SIFT as a "deleterious" variant and a Grantham score of 60. The evolutionary model of variant effects yielded a high EVE score of 0.966 [27]. The

other predictor scores were as follows: REVEL: 0.776; CADD: 23.5; and PrimateAI: 0.575. AlphaMissense was benign. Varsome tools classify the variant as in silico predictors BP4: benign strong, with the use of the ACMG criteria, the main reason for being benign is its high frequency in population databases, compared with the disease prevalence [28].

Because the variant p.G545A is so common, it cannot be regarded as a monogenic cause of renal disease but could be considered a predisposing or risk factor rather than a pathogenic variant. Also, one cannot exclude the possibility that it acts as a genetic modifier in the presence of another pathogenic or likely pathogenic variant, either in cis or in trans.

In the Greek Cypriot population, we found that the p.G545A variant was significantly more common in patients referred for testing because of hematuria (n = 468) than in controls in the general population (n = 368), p = 0.037. On the other hand, COL4A4:p.G545A, either demonstrates incomplete penetrance or it acts as a genetic factor conferring higher predisposition to hematuria and CKD rather than as a causative mutation following a Mendelian inheritance (Deltas C and colleagues, unpublished results).

With regard to functional studies, a recent publication reports experiments in transiently transfected cells in culture, with the use of a dual luciferase assay to examine the efficiency of secretion of different mutant collagen trimers [29]. Different glycine substitutions in the collagen IV alpha chains demonstrated disparate abnormalities, with the p.G545A variant demonstrating minimal but distinct impaired secretion, compared with wild type molecules. We can hypothesize that the p.G545A variant is highly hypomorphic, with adequate residual activity, which only occasionally associates with CKD in a non-Mendelian fashion, and only in the presence of other genetic or environmental factors or a combination of these, which largely remain unknown.

The major limitation of the study is that although we expected to find that variants in COL4A3/4/5 were common we have not found this. We have not been able to investigate more families with WES, or compare with populations without renal disease and it was not possible to obtain more genetic information for most patients. More extensive genetic investigation is required to exclude deletions, insertions, copy number variation and intronic variants in these genes. Electron microscopy from more cases would be informative although CKD is often advanced before it is recognized and renal biopsy not performed.

In summary, we identify glycine substitution in *COL4A4* that we propose is highly hypomorphic with adequate residual activity. It is common in all populations studied (precluding its classification as a Mendelian disease-causing pathogenic variant) but is significantly enriched among Turkish Cypriots and with evidence of kidney disease that is usually characterized by tubulointerstitial, rather than glomerular, clinical features.

Given its frequency in Eastern Mediterranean populations and its statistically significant enrichment among Turkish Cypriot families with kidney disease, this may represent a contributor to increased risk of renal failure that is well documented in the Eastern Mediterranean Region, with familial clustering reminiscent of *APOL1* mediated kidney disease that is endemic in some African populations [30]. Identified *APOL1* variants do not cause a disease with Mendelian inheritance but they confer high predisposition to those carrying it, as documented by numerous studies in African populations where it is most prevalent. Further studies will be needed to determine if the pathology relates to variants in Alport genes, and how intersection of various polygenic, common and uncommon genetic risk factors for kidney disease interact in individuals, families, and populations.

Acknowledgments

We would like to thank the families included in the study. We also thank Dr. Huseyin Sevay for his help with the pedigree drawings. An earlier preprint version of this article is available on Researchsquare.com https://doi.org/10.21203/rs.3.rs-2844330/v2 Fezile Ozdemir, D Deren Oygar, Ahmet Behlul, Salahi Ataç, Simge Bardak, Meral Yükseliş, Gregory Papagregoriou, Apostolos Malatras, Daniel P Gale, Guy H Neild, Constantinos Deltas, Cemal Gurkan. AD kidney disease phenocopying hypertensive nephropathy in Turkish Cypriot Families.

Statement of Ethics

Written informed consent was obtained for participation in this study. All samples collections were performed with written informed consent and in accordance with the ethical principles for medical research involving human subjects and according to the Declaration of Helsinki of the World Medical Association. This study was approved by the northern Cyprus Ministry of Health Ethics Committee [Decision Number YTK.1.01 (Ek 002/19)]. For the work performed at the biobank.cy Center of Excellence in the Republic of Cyprus (EU), there was no ethics approval sought as all the samples used were under complete anonymity.

Conflict of Interest Statement

The following authors declare no competing interests: F.O., D.D.O., A.B., S.A., S.B., M.Y., G.P., A.M., C.D., C.G., or G.H.N. Prof. D.P.G. was a member of the Journal's Editorial Board at the time of submission.

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Author Contributions

Research idea and study design: D.D.O. and G.H.N.; clinical care, data, and sample collection: D.D.O., A.B., S.A., S.B., M.Y., and F.O.; laboratory studies: F.O. and C.G.; data analysis/interpretation: F.O., G.P., G.H.N., D.P.G., and C.G.; statistical analysis: A.M., G.P., D.P.G., and C.D.; manuscript writing: G.H.N., C.D., D.P.G., C.G., and F.O.

Data Availability Statement

The data that support the findings of this study are not publicly available as they contain information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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