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Contribution of Recessive Ciliopathy Genes in a Highly Consanguineous Adult Cohort with Biopsy-Proven Focal Segmental Glomerulosclerosis

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Abstract

Background

Focal segmental glomerulosclerosis (FSGS) is a leading cause of nephrotic syndrome in adults and frequently progresses to end-stage renal disease. Emerging evidence suggests recessive ciliopathy genes contribute to glomerular disease, particularly in consanguineous populations, but their role in adult biopsy-proven FSGS remains incompletely defined. This study aimed to determine the frequency and clinical impact of pathogenic variants in recessive ciliopathy genes among adults with FSGS from a highly consanguineous Middle Eastern population.

Methods

We conducted a case-control study including 35 adults with biopsy-proven FSGS and 20 unaffected individuals with normal kidney function from Sulaymaniyah, Iraq. All participants underwent targeted next-generation sequencing of a 98-gene panel on the Ion S5 platform. Variants were classified according to 2015 American College of Medical Genetics and Genomics (ACMG) criteria; only pathogenic (P) and likely pathogenic (LP) variants in recessive ciliopathy genes were analyzed. Formal rare-variant burden analysis was performed. Demographic and clinical data were compared between groups.

Results

Biallelic ciliopathy variants were identified in 16 of 35 FSGS patients (45.7%) versus 0 of 20 controls ($p < 0.001$; OR 34.7, 95% CI 1.9-618.7). Seven ciliopathy genes were implicated: INPP5E (10 patients, 28.6%), BBS2 (7 patients, 20.0%), CPLANE1 (6 patients, 17.1%), CEP290 (4 patients, 11.4%), TCTN2 (1 patient), BBS7 (1 patient), and NPHP3 (1 patient). All identified variants were absent or ultra-rare (allele frequency < 0.000007) in gnomAD v4.1, confirming their rarity. Ciliopathy-positive patients demonstrated universal proteinuria, higher rates of hematuria (81.3% vs 21.1%, $p < 0.001$), more severe renal dysfunction (serum creatinine 3.6 ± 0.9 vs 1.2 ± 0.4 mg/dL, $p < 0.001$), and increased hypertension prevalence (68.8% vs 31.6%, $p = 0.002$) compared with ciliopathy-negative FSGS patients.

Conclusions

In this highly consanguineous Middle Eastern cohort, recessive ciliopathy gene variants, particularly in INPP5E, BBS2, and CPLANE1, were frequent among adults with biopsy-proven FSGS and associated with severe progressive kidney disease. These findings support incorporating ciliopathy gene testing into the diagnostic evaluation of adults with FSGS from consanguineous families or with positive family history of kidney disease.

1. Background

Focal segmental glomerulosclerosis (FSGS) represents a clinically and genetically heterogeneous kidney disorder characterized by sclerosis of some glomeruli with involvement of portions of affected glomeruli (1). FSGS accounts for approximately 40% of cases of adult nephrotic syndrome and leads to end-stage renal disease (ESRD) as a major worldwide cause (2–4). This clinical heterogeneity reflects diverse underlying mechanisms including podocytopathies, secondary forms, and monogenic causes.(3, 5, 6).

More than 50 monogenic FSGS genes have been identified, including podocyte structural genes (NPHS1, NPHS2, WT1, LAMB2, CD2AP, TRPC6) and collagen IV genes (COL4A3–COL4A5), which typically underlie early-onset or familial disease (5–10).

FSGS has not been the subject of detailed genetic analysis because the genes encoding the proteins of the primary cilium and centrosome are not fully understood (11, 12). The primary cilium is a signaling organ responsible for maintaining cellular homeostasis. Mutations in cilia function impair numerous critical processes required for normal glomerular development and maintenance of the filtration barrier. The recent identification of mutations in the TTC21B gene leading to late-onset familial FSGS due to intraflagellar transport defects established that ciliopathies are responsible for more than just congenital and developmental kidney diseases(11, 13, 14).

In subsequent reports, other multiple ciliopathy genes carrying mutations that are also associated with FSGS have been described. CEP290 mutations that cause Joubert syndrome/nephronophthisis have been described in patients with FSGS (15–17). Similarly, CC2D2A mutations are also associated with FSGS with nephronophthisis overlap (15). The Joubert syndrome/MORM syndrome causing mutation in INPP5E gene a ciliary protein essential for intraflagellar transport has not yet been described in confirmed cases of FSGS (18–20). BBS2 and BBS7 along with other BBS genes necessary for BBSome complex biogenesis involved in cilia formation have also been identified as genes responsible for causing glomerular disease (21–24)

Consanguineous marriages result in an increased chance of homozygous mutations and therefore an increased expression of recessive genes responsible for ciliopathies (25, 26). Ciliopathies and other recessive genetic disorders are over-represented in Middle Eastern and North African populations where consanguinity rates are estimated to be above 20% (27–29).

This study employed the occurrence of mutations in ciliary genes in a cohort of 35 adult FSGS patients and 20 controls from a highly consanguineous population. Using targeted Next Generation Sequencing (NGS) of a 98 gene panel we found pathogenic mutations in 16 cases (45.7%) confirming the relevance of mutations in ciliary genes in the etiology of FSGS in this population. We describe the clinical and genetic heterogeneity of mutations and contrast them with those identified in controls. These data highlight the importance of the sequencing of ciliary genes in adult patients with FSGS, particularly in cases with a positive family history and/or consanguinity.

2. Methods

2.1 Study Population

35 adult patients with FSGS confirmed by kidney biopsy and 20 controls from the healthy population of Sulaymaniyah, Iraq, with normal kidney function. This study population included FSGS patients whose biopsy kidneys were evaluated by light microscopy (LM) and immunofluorescence and electron microscopy. Patients were excluded if their FSGS was associated with lupus or vasculitis or if it was drug-associated, and obesity-associated glomerulosclerosis. Control Individuals: Healthy controls had: (i) normal serum creatinine (ii) no proteinuria (urine protein <0.15 g/24 hours); (iii) normal blood pressure (<130/80 mmHg); (iv) no personal or family history of kidney disease.

2.2 Ethics approval and consent to participate

The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. Ethical approval was given by the Research Ethics Committee of University of Sulaymaniyah, Kurdistan Region, Iraq. Written informed consent was obtained from all participants. Written informed consent was obtained from the parents or guardians of children less than 18 years old.

2.3 Clinical and Laboratory Assessments

Patient characteristics at the time of biopsy were recorded including age, sex, family history of kidney disease and parental consanguinity. Additional baseline information included serum creatinine and blood urea nitrogen levels (all in mg/dL), protein in urine, dipstick hematuria ≥1+ and blood pressure measured and history of previous kidney transplant.

2.4 Genetic Analysis and Sequencing

DNA from peripheral blood leukocytes was extracted from patients using a Wizard® Genomic DNA Purification Kit (Promega, Madison, WI, USA). A custom panel of 98 genes was designed using the Ion AmpliSeq Designer software (v6.2; Thermo Fisher Scientific) with respect to the hg19/GRCh37 genome assembly. The genes included in this panel NPHP1, NPHP3, CEP290, TMEM67, BBS1, BBS2, BBS7 and INPP5E, TCTN1–3, CC2D2A and many others. DNA libraries were then prepared using the Ion AmpliSeq Library Kit 2.0 and sequenced on an Ion Torrent S5 (Thermo Fisher Scientific) platform with Ion 540 chips as recommended by the manufacturer. The custom panel contained 2,742 amplicons of length between 125 and 275 bp distributed in two primer pools and it provided in silico 99% coverage of coding exons and exon–intron boundaries. The mean depth of coverage for all genes was over 200× and more than 98% of the targeted bases had a coverage of at least 20×.

2.5 Variant Annotation and Classification

All sequencing data was analyzed using Torrent Suite Software from Thermo Fisher Scientific. After primer trimming and read alignment to the hg19/GRCh37 reference genome using TMAP, the Torrent Variant Caller with parameters of 5% minimum variant allele fraction (VAF) and 100× minimum read depth was used to call variants. Annotation was performed using the Franklin platform from Genoox, which integrates population data from gnomAD v4.1, 1000 Genomes and ExAC, as well as prediction scores from SIFT, PolyPhen-2, CADD, FATHMM, MutationTaster scores, PhyloCSF and GERP conservation scores. MAF in any of the gnomAD v4.1 populations was required to be ≤0.0001 and we were cautious when including Middle Eastern and North African populations to avoid including regional polymorphisms. Variants were classified as pathogenic (P), likely pathogenic (LP), variant of uncertain significance (VUS), likely benign, or benign according to the 2015 ACMG guidelines (30). All subsequent analyses were performed using only P and LP variants, with VUS, likely benign, and benign variants excluded. The variants identified here have been submitted to ClinVar (NCBI) and are available under accession numbers **SCV007520383–SCV007520396**. The transcript and HGVS nomenclature of the P/LP variants, their zygosity, the number of affected patients and the corresponding allele frequencies in the gnomAD v4.1 are shown in Supplementary Table S1.

2.6 Statistical Analysis

All values are given as means ± SD. For comparison of continuous variables, independent-samples t-test or one-way ANOVA was used. For categorical variables, the data were presented as the number and percentage and the chi-square or Fisher's exact test was used. All the tests were two tailed and $p < 0.05$ was considered to be statistically significant. We identified carriers to be those with ≥1 P or LP variants in any of the ciliopathy genes in a homozygous (biallelic) configuration as predicted by the AR pattern of inheritance for FSGS. We calculated the OR and 95% CI (Haldane correction) to compare the carrier status versus FSGS using Fisher's exact test. In addition, gene-specific burden tests for INPP5E, BBS2, CPLANE1 and CEP290 were carried out. The frequency of the identified alleles/alternate bases within the genome aggregation database v4.1 (gnomAD v4.1) and their confirmed rarity, particularly in Middle Eastern and North African populations, was verified for pathogenicity of the identified variants. The SPSS v25.0 statistical software (IBM Corp., Armonk, NY, USA) and Python 3.9 (SciPy library) were used for these analyses. The exploratory gene-specific p-values are provided without adjustment. With four gene-specific burden tests being carried out, the Bonferroni adjustment for a threshold of $\alpha = 0.0125$ is required.

3. Results

3.1. Study Cohort Characteristics

35 adults with biopsy-proven FSGS and 20 healthy controls were studied in this cohort (Table 1). The mean age at diagnosis of FSGS was 25.1 ± 7.9 years (range 14–52). Eighty percent of FSGS patients (28/35) were from consanguineous families, which is higher than none of the controls (0/20; $p<0.001$).

Pathogenic or likely pathogenic variants in genes encoding subunits of the cilia were identified in 16 of 35 FSGS patients (45.7%) and in 0 of 20 controls (p<0.001). Clinical characteristics of Ciliopathy positive FSGS patients had universal proteinuria (16/16, 100%) and frequent hematuria (13/16, 81.3%). They had a significantly worse renal function (higher serum creatinine levels, 3.6 ± 0.9 vs 1.2 ± 0.4 mg/dL; BUN, 76.4 ± 31.2 vs 29.7 ± 10.5 mg/dL) and higher ESRD performed transplantation rates (31.3% vs 10.5%) than the ciliopathy negative patients with FSGS.

Table 1. Demographic, Clinical, and Laboratory Characteristics of Study Participants

Characteristic	FSGS Ciliopathy-Positive (n=16)	FSGS Ciliopathy-Negative (n=19)	Healthy Controls (n=20)	P-value
Age, years (mean ± SD, range)	25.1 ± 7.9 (14–52)	27.4 ± 8.1 (16–48)	26.8 ± 7.5 (18–45)	NS
Male/Female, n	10/6	11/8	12/8	NS
Clinical Features				
Consanguinity, n (%)	13 (81.3)	3 (15.8)	0 (0)	<0.001
Family history of kidney disease, n (%)	16 (100)	5 (26.3)	0 (0)	<0.001
Laboratory Parameters at Baseline				
Serum creatinine, mg/dL (mean ± SD)	3.6 ± 0.9	1.2 ± 0.4	0.8 ± 0.2	<0.001
Blood urea nitrogen, mg/dL (mean ± SD)	76.4 ± 31.2	28.3 ± 12.1	16.2 ± 5.8	<0.001
Proteinuria ≥0.5 g/24 hr, n (%)	16 (100)	5 (26.3)	0 (0)	<0.001
Hematuria (dipstick ≥1+), n (%)	13 (81.3)	4 (21.1)	0 (0)	<0.001
Clinical Outcomes				
Hypertension, n (%)	11 (68.8)	6 (31.6)	0 (0)	0.002
ESRD/Kidney transplant, n (%)	5 (31.3)	2 (10.5)	0 (0)	0.053

NS, not significant; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate.

3.2. Rare-Variant Burden Analysis

To assess the degree of enrichment of recessive ciliopathy variants we performed gene set burden testing on the biallelic pathogenic/likely pathogenic carrier status. Of the 35 FSGS patients, 16 (45.7%) were carriers, compared to 0 of the 20 controls (Fisher's exact p<0.001) giving an odds ratio of 34.7 (95% CI 1.9–618.7) after Haldane correction. The distribution of these recessive ciliopathy genes among FSGS patients is shown in Figure 1. Gene specific burden tests for INPP5E, BBS2, CPLANE1 and CEP290 are shown in (Supplementary Table S2). There is enrichment for INPP5E (10/35 cases vs 0/20; OR 17.0, 95% CI 1.0–294.0; p=0.011) and BBS2 (7/35 vs 0/20; OR 10.7, 95% CI 0.6–199.5; p=0.053). There is weaker evidence for carrier status for CPLANE1 (6/35; p=0.076) and CEP290 (4/35; p=0.285). The wide CI are due to the small number of cases in this analysis and the fact that we have not identified any carriers in the control cohort, so we simply treat the gene level p values as hypotheses to be tested in larger data sets. Further studies with larger multi-center cohorts will be needed to confirm our observation of an enrichment of ciliopathy variants in adult FSGS.

Sequencing data were re analyzed from over 730,000 individuals in gnomAD v4.1 and examined the prevalence of the common frameshift mutations in INPP5E and BBS2 as well as all reported truncating mutations in CPLANE1. The INPP5E c.367_368delGC (p. Ala123ProfsTer27) mutation that results in a premature stop codon at c.385 (p. Ala123ProfsTer27)) was present in homozygote form in all 10 FSGS individuals carrying an INPP5E mutation, was not present in gnomAD or in the exomes of any of the individuals in the Middle Eastern populations. The 3 BBS2 frameshift mutations c.1254delT, c.1725delT, c.106_107delCA as well as 5 of the reported CPLANE1 frameshift mutations were not present or were found to be ultra rare (AF < 0.000007) as were variants in CEP290, TCTN2, BBS7 and NPHP3.The universal absence or extreme rarity of these truncating mutations, and the fact that they are present in homozygote form only in individuals with FSGS confirms their role as pathogenic mutations in this disease.

3.3. Genetic Findings: Spectrum of Ciliopathy Mutations

Targeted panel sequencing identified 16 of 35 FSGS patients (45.7%) with pathogenic or likely pathogenic ciliopathy variants. The 35 pathogenic/likely pathogenic variant alleles were detected in 16 individuals; 15 frameshift mutations were identified, and all were truncating (100%). Using the ACMG 2015 standards, 6 variants (40.0%) were classified as pathogenic, and 9 (60.0%) as likely pathogenic. There were no VUS, likely benign, or benign variants that were retained in these patients who had variants in the ciliopathy genes.

3.3.1 Ciliopathy Gene Variant Frequency and Spectrum

The 16 ciliopathy-positive patients carried variants in seven genes: INPP5E, BBS2, CPLANE1, CEP290, TCTN2, BBS7, and NPHP3 (Table 2). Mutations in INPP5E were identified in 10 of 16 ciliopathy positive patients (62.5%) and in 5 of 18 (28.6%) of the full FSGS cohort. All carried the same homozygous frameshift mutation c.367_368delGC (p.Ala123ProfsTer27) which is a population specific founder mutation. Mutations in BBS2 were present in 7 of 16 (43.8%; 20.0% of the full FSGS cohort) ciliopathy positive patients and were identified as three frameshift mutations; c.1254delT, c.1725delT and c.106_107delCA which were all present in biallelic combinations. CPLANE1 variants occurred in 6 of 16 ciliopathy-positive patients (37.5%; 17.1% of the

cohort) across five frameshift alleles (c.1819delT, c.1868_1869insT, c.8263delA, c.6599delT, c.3912delA). CEP290 variants were detected in 4 patients (11.4% of the cohort), TCTN2 in 1 patient, and BBS7 and NPHP3 in 1 patient each. Complete variant information, including ACMG classification, number of patients carrying each allele, and gnomAD v4.1 allele counts and frequencies, is presented in Table 3 and Supplementary Table S1.

3.4 Association between ciliopathy genes and genotype–phenotype correlations

3.4.1 Age at FSGS diagnosis and clinical presentation

There was no statistically significant difference in age at diagnosis between genes ($p > 0.05$, Table 2). INPP5E, BBS2, CEP290 and CPLANE1 mutations typically presented in early to mid-twenties, while BBS7 and NPHP3 cases presented in their thirties, more in keeping with adult onset FSGS than childhood podocytopathy.

3.4.2 Biochemical parameters: serum creatinine and urea

Baseline renal function was associated with the expression of the gene encoding creatinine and BUN ($p < 0.001$ and $p < 0.05$, respectively, (Tables 2). The highest levels of BUN were recorded for the INPP5E, CPLANE1 and BBS2 genes, while the lowest BUN values were recorded for the CEP290, NPHP3 and BBS7 genes. These values corresponded to those recorded for creatinine, indicating that the extent of renal impairment was gene-specific.

3.4.3 Proteinuria and hematuria

Proteinuria was present in all 16 ciliopathy positive patients, compared to 26.3% of ciliopathy negative FSGS patients and none of the controls (both $p<0.001$). Hematuria was also more common in ciliopathy positive patients (81.3% vs 21.1% and 0%; $p<0.001$), particularly in CEP290, TCTN2, BBS7 and INPP5E mutation carriers.

3.4.4 Hypertension and transplant outcomes

Hypertension was more common in ciliopathy positive than ciliopathy negative individuals (68.8% vs 31.6%; $p=0.051$) and was not detected in controls ($p<0.001$). Kidney transplantation for ESRD had occurred in 31.3% of ciliopathy positive individuals and 10.5% of ciliopathy negative individuals, with no further transplants recorded.

Table 2. Genotype-Phenotype Correlations by Ciliopathy Gene

Gene	Patients (n)	Variants (n)	Unique Mutations	Age at Dx (yr)	Creatinine (mg/dL)	BUN (mg/dL)	Consanguinity (%)	Family Hx (%)	Hematuria (%)	Hypertension (%)
INPP5E	10	10	c.367_368delGC	23.2±8.4	4.0±1.3	88.6±25.3	33.3	77.8	88.9	22.2
BBS2	7	9	c.1254delT c.1725delT c.106_107delCA	27.3±4.1	3.8±0.4	80.3±12.8	28.6	75.0	71.4	33.3
CPLANE1	6	9	c.8263delA c.1868_1869insT c.1819delT c.6599delT c.3912delA	29.3±10.8	3.7±2.3	88.5±38.9	66.7	100	33.3	50.0
CEP290	4	4	c.2462delT c.6416_6417delAA c.2523delA	24.8±6.9	1.8±0.8	45.6±20.1	50.0	75.0	100	0
TCTN2	1	1	c.1206delT	23.0	2.5	68.5	100	100	100	0
BBS7	1	1	c.1759_1760delAG	30.0	4.0	52.0	0	100	100	0
NPHP3	1	1	c.2161delA	30.0	4.0	44.0	100	100	33.3	0

Dx, diagnosis; BUN, blood urea nitrogen; Hx, history

3.5. Inheritance Patterns and Consanguinity

All 16 patients with FSGS that were found to have mutations in the genes associated with ciliopathy had biallelic mutations (Table 3). Consanguinity was reported in 81.3% of the ciliopathy positive patient's vs 15.8% of the ciliopathy negative FSGS patients ($p<0.001$) a 5.3-fold enrichment. Consanguinity rates for each gene were as follows: all carriers in the TCTN2 and NPHP3 cohorts were consanguineous and although the consanguinity rate for CPLANE1 carriers was not as high at 66.7%, it was still clearly present. For INPP5E, CEP290 and BBS2 carriers, consanguinity rates were present but were lower. There was only

one patient with a BBS7 mutation and they had no reported family relationships but because of the small number of carriers this was not felt to be statistically significant.

Table 3. Detailed Variant Classification and ACMG Annotation

Gene	Transcript	cDNA Change	Protein Change	Mutation Type	ACMG Class	Number of Patients	Inheritance
INPP5E	NM_019892.6	c.367_368delGC	p.Ala123ProfsTer27	Frameshift deletion	LP	10	AR
BBS2	NM_031885.5	c.1254delT	p.Phe418LeufsTer40	Frameshift deletion	LP	6	AR
BBS2	NM_031885.5	c.1725delT	p.Phe575LeufsTer8	Frameshift deletion	P	2	AR
BBS2	NM_031885.5	c.106_107delCA	p.Gln36AsnfsTer8	Frameshift deletion	LP	1	AR
CPLANE1	NM_023073.3	c.8263delA	p.Thr2755HisfsTer2	Frameshift deletion	P	1	AR
CPLANE1	NM_023073.3	c.1819delT	p.Tyr607ThrfsTer6	Frameshift deletion	P	3	AR
CPLANE1	NM_023073.3	c.1868_1869insT	p.Leu623PhefsTer8	Frameshift insertion	LP	3	AR
CPLANE1	NM_023073.3	c.6599delT	p.Leu2200CysfsTer85	Frameshift deletion	LP	1	AR
CPLANE1	NM_023073.3	c.3912delA	p.Gly1305GlufsTer13	Frameshift deletion	LP	1	AR
CEP290	NM_025114.4	c.2462delT	p.Leu821CysfsTer7	Frameshift deletion	LP	2	AR
CEP290	NM_025114.4	c.6416_6417delAA	p.Lys2139SerfsTer3	Frameshift deletion	LP	1	AR
CEP290	NM_025114.4	c.2523delA	p.Glu842ArgfsTer15	Frameshift deletion	LP	1	AR
TCTN2	NM_024809.5	c.1206delT	p.Phe402LeufsTer12	Frameshift deletion	LP	1	AR
BBS7	NM_176824.3	c.1759_1760delAG	p.Arg587GlufsTer3	Frameshift deletion	LP	1	AR
NPHP3	NM_153240.5	c.2161delA	p.Met721Ter	Frameshift deletion	LP	1	AR

ACMG, American College of Medical Genetics and Genomics; P, pathogenic; LP, likely pathogenic; AR, autosomal recessive. Summary: Total distinct variants identified: 15 (all frameshift mutations). Pathogenic (P): 6 (40.0%). Likely pathogenic (LP): 9 (60.0%).

4. Discussion

4.1. Overview and key messages

This study indicates that recessive ciliopathy gene variants are important contributors to adult FSGS in this highly consanguineous cohort. Mutations in genes encoding ciliopathy proteins were identified in 45.7% of FSGS patients but none of the controls, and all 35 alleles contained truncating pathogenic/likely pathogenic mutations according to ACMG guidelines. Ciliopathy positive patients had more severe disease: universal nephrotic range proteinuria, hematuria, worse renal function, more consanguinity and family history suggestive of recessive inheritance and thus a significant association between mutations in ciliopathy genes and adult FSGS in this patient group.(31, 32).

Research on FSGS sequencing has shown that monogenic causes exist in 10-40% of cases which primarily affect patients with steroid-resistant disease, those who develop the condition at young ages and have family history of the disease(33, 34). The studies focused on two gene groups which include podocyte structural genes (NPHS1, NPHS2, ACTN4, TRPC6) and collagen IV genes(5, 32, 35). Research on ciliopathy genes has focused primarily on their role in developmental renal disease and cystic nephronophthisis instead of their role as the main factor in adult FSGS (36, 37). Our results extend this paradigm by showing that, at least in a consanguineous Middle Eastern cohort, recessive ciliopathy genes form one of the largest identifiable genetic categories of FSGS and can present with a “pure” glomerular phenotype.

We recently demonstrated by rare variant burden analysis an enrichment of bi-allelic recessive ciliopathy variants in our FSGS cases compared to controls (OR 34.7, 95% CI 1.9–618.7, p<0.001), which suggests a major genetic role for ciliopathy in our data set. Of the 34 bi-allelic recessive ciliopathy variants detected, the 3 genes with the highest enrichment scores were INPP5E, BBS2 and CPLANE1, with INPP5E and BBS2 having p values of less than 0.005. All variants were absent or ultra rare in the gnomAD v4.1 exome data set (MAF <0.000007) including in Middle Eastern populations, thus common polymorphisms can be ruled out.

4.2. Gene-specific patterns: INPP5E, BBS2, CPLANE1 and others

Mutations in the INPP5E gene were the most common mutations identified in this group of patients. All 10 INPP5E mutant carriers had the homozygous c.367_368delGC (p.Ala123ProfsTer27) mutation and this allele was not detected in the control population. INPP5E carriers had the highest average serum creatinine and urea levels and also the highest rate of hematuria (88.9%). The age of onset of the kidney disease was variable and ranged from the second to the third decade of life. INPP5E mutations are associated with Joubert syndrome, MORM (mental retardation, ocular malformations, microcephaly, skeletal abnormalities) syndrome and kidney disease. Our data suggests that mutations in INPP5E can also cause adult onset FSGS with significant renal injury in a consanguineous family**.** (38-40).

BBS2 mutations were found in 7 patients (3 different frameshift mutations: c.1254delT, c.1725delT and c.106_107delCA) with ciliopathy. Patients with BBS2 mutations had heavy proteinuria, elevated serum creatinine, more frequently hematuria and hypertension compared to INPP5E patients. Mutations in BBS2 encode a subunit of the BBSome complex. BBSome mutations were identified in patients with Bardet–Biedl syndrome (BBS), our adult patients with biallelic mutations in BBS2 did not show any clinical features suggestive of the BBS syndrome suggesting that the renal phenotype in adult patients with mutations in the BBSome may be more pronounced and dominant over any possible limited or non-obvious extra-renal manifestations.(41, 42).

Ciliopathy genes in our cohort, including CPLANE1, CEP290, TCTN2, BBS7 and NPHP3, demonstrated consistent associations with reduced renal function and FSGS biopsy proven disease. The classical nephronophthisis related ciliopathy syndromes caused by mutations in STK11/LKB1, CTNS and TTC21B genes are characterized by tubulointerstitial fibrosis, cysts and bland urinalysis with minimal proteinuria and hematuria in late-stage kidney disease. Patients carrying mutations in STK11 and TTC21L in the CEP290 locus uniformly developed proteinuria, and also hematuria in some cases within the CEP290 positive subgroup, indicating early onset kidney disease characterized by glomerular dysfunction with increased permeability to proteins and cells. Our findings, together with earlier reports of FSGS linked to ciliary genes, such as TTC21B, NPHP4, CRB2 and CC2D2A, suggest that disrupted function of distinct ciliary modules may give rise to a unifying glomerular disease process that manifests as FSGS and podocyte damage.(13, 37, 43-45).

4.3. Pathophysiologic implications

Primary cilia have been implicated in signaling in podocytes and also in cytoskeletal organization(46, 47). These common features of the 35-truncating LOF mutations and the uniform FSGS histology and severe proteinuria suggest that mutations in these genes destabilize the podocyte and lead to disruption of the filtration barrier. Gene-specific functions may also contribute to the observed phenotypic heterogeneity of mutations within a gene. For example, mutations in genes encoding ciliary proteins involved in signaling (such as INPP5E and CEP290) were associated with more hematuria suggesting more extensive damage to the endothelium, GBM and/or podocytes. In contrast, mutations in CPLANE1, a component of the transition zone complex, were most commonly found in patients with universal proteinuria but relatively little hematuria, suggesting an important role of this protein in the maintenance of the structure and function of the foot processes and slit diaphragm of the podocyte. The mutations in BBS2/BBS7 may contribute to the relative resistance of the podocyte to signals from vasopressin and other molecules, blood pressure and thereby to the development of hypertension and progression of the renal disease. (36, 37, 48).

4.4. Clinical implications and genetic testing strategy

Genetic testing for an expanded panel of ciliopathy genes in adult patients with FSGS revealed disease causing mutations in a subset of consanguineous families. Single gene panel testing for NPHS and COL4A genes may not detect mutations present in certain populations, indicating that the use of broad panels of genes is required and that single gene sequencing may not be sufficient in some cases (35).

Genetic testing can help identify biallelic mutations in ciliopathy genes and thus lead to a definitive diagnosis for affected individuals and their families. This test is not immunology dependent and is autosomal-recessive as each of the children of an affected parent will have a 25% chance of developing the disease. This test may be also helpful to determine if an individual is a carrier and to facilitate family planning especially in large families. The identification of mutations in a gene that leads to the diagnosis of the renal disease associated with ciliopathy genes will also allow complete cascade testing for possible extra renal features of the disease including neurological, ocular, skeletal and endocrine (49). Early genetic testing can be used in patients with suspected hereditary FSGS for diagnosis and clinical management (50, 51).

4.5. Limitations and future directions

While the cohort is small, it is the first study to our knowledge to examine the role of recessive ciliopathy genes in adult FSGS in a highly consanguineous cohort from a Middle Eastern population. The strong enrichment of biallelic truncating mutations in affected individuals relative to controls supports an association. However, there are limitations to this study. The cohort was small (35 cases and 20 controls) and examination of some of the genes (BBS7, NPHP3 and TCTN2) had only a single affected individuals per gene which may not provide sufficient power to make any gene-specific genotype-phenotype association. Genotype-phenotype analyses were performed in without multivariable adjustment because of insufficient power for multiple regression analyses to account for any potential confounders. Rare variant burden analyses were performed in an unadjusted fashion and only Haldane corrected gene level p values were reported because of multiple testing. The overall burden analysis between cases and controls seemed robust, but should be interpreted with caution at the gene level, particularly when the p values are close to the multiple testing threshold such as BBS2 and CPLANE1. A major limitation is that this is a cross-sectional study, and we do not capture the natural history of the disease such as time to ESRD and to kidney transplantation as well as post-transplant outcomes. We did not also perform a detailed evaluation of extra-renal manifestations (neuroimaging, ophthalmology, audiology and endocrinology). Thus, it is possible that subtle manifestations of ciliopathy have been overlooked. Lack of consanguinity between affected individuals and their extended family members meant that we were not always able to perform segregation analysis and Sanger confirmation, which would have allowed us to further demonstrate co-segregation. However, the presence of biallelic truncating mutations in affected individuals with complete absence or near absence of the variants in gnomAD in the context of consanguinity provides compelling evidence of their pathogenicity. A multi-center study that includes affected individuals with different ages at diagnosis, in addition to a larger control cohort, will be required to assess gene-specific risks of disease, as well as including more comprehensive extra-renal evaluation and functional in vitro or in vivo assays to better understand the disease-causing pathways at the level of cilia biology, e.g. roles of INPP5E, CPLANE1 and CEP290 in FSGS.

5. Conclusions

Mutations in ciliopathy genes appear to be important genetic contributor for adult FSGS in highly consanguineous populations. In this study, biallelic pathogenic or likely pathogenic variants were identified in 45.7% of patients and mutations in INPP5E, BBS2 and CPLANE1 were identified accounting for

most genetically explained cases. In conclusion, mutations in ciliopathy genes should be considered in the genetic testing panel for adult FSGS, particularly in consanguineous families and those with strong family history of kidney diseases.

Abbreviations

ACMG: American College of Medical Genetics and Genomics
BBS: Bardet-Biedl syndrome
BUN: Blood urea nitrogen
CI: Confidence interval
eGFR: Estimated glomerular filtration rate
ESRD: End-stage renal disease
FSGS: Focal segmental glomerulosclerosis
gnomAD: Genome Aggregation Database
LP: Likely pathogenic
MAF: Minor allele frequency
NGS: Next-generation sequencing
OR: Odds ratio
P: Pathogenic
SD: Standard deviation
VUS: Variant of uncertain significance

Declarations

Ethics approval and consent to participate

The research team executed their study based on Declaration of Helsinki guidelines and Good Clinical Practice standards. Ethical approval was obtained from the Research Ethics Committee of the University of Sulaymaniyah, Kurdistan Region, Iraq. All study participants received written informed consent before starting the research but participants under 18 required their parent or legal guardian to give consent.

Consent for publication

Not applicable. The manuscript does not contain any identifiable individual data or images.

Availability of data and materials

The pathogenic and likely pathogenic variants identified in this study have been deposited in ClinVar, a publicly accessible database of human genetic variation and its relationship to health (NCBI ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/). The variants are available under accession numbers SCV007520383–SCV007520396 and can be accessed via our submitter page, Molecular Lab (submitter ID 510454), at: https://www.ncbi.nlm.nih.gov/clinvar/submitters/510454/.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Lava I. Ahmed conceived and designed the study, obtained ethical approval, supervised the research, performed DNA extraction, library preparation and next-generation sequencing, conducted statistical analysis, and drafted the manuscript.

Dlnya A. Mohammed, MD, PhD contributed to study design, supervised laboratory work, assisted in data interpretation, and critically reviewed and revised the manuscript.

Dana Ahmed Sharif, MD recruited patients, collected and managed clinical data, reviewed kidney biopsy reports, and contributed to clinical interpretation of genotype–phenotype correlations.

All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Figures

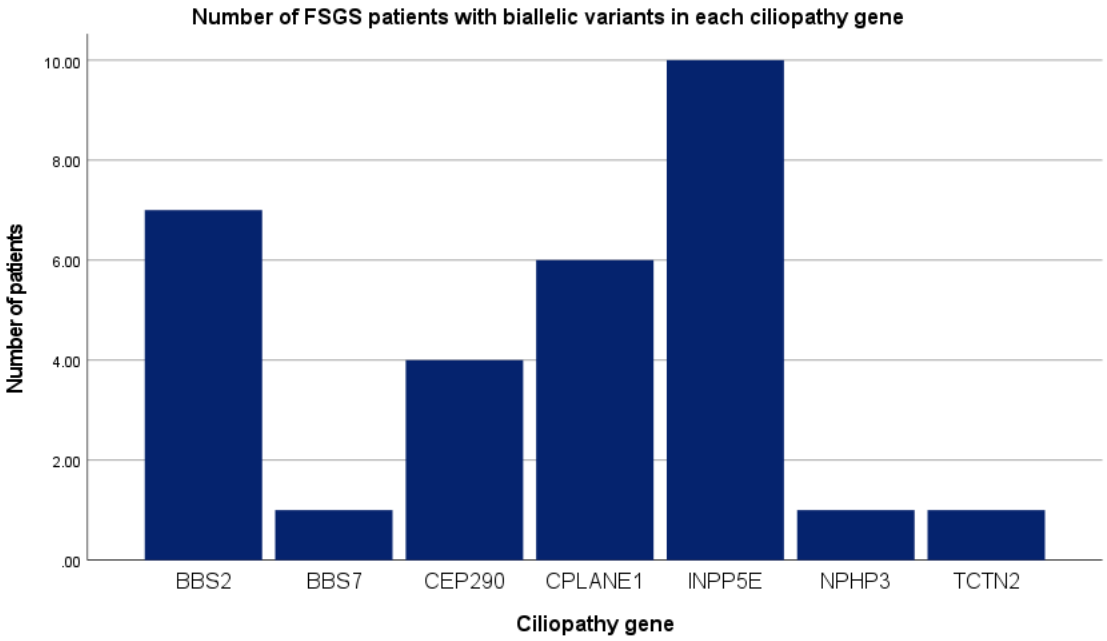


Figure 1

The number of adults with FSGS confirmed by kidney biopsy and with confirmed biallelic pathogenic or likely pathogenic variants in the listed recessive ciliopathy genes.

Supplementary Files

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