ADCK4-Associated Glomerulopathy Causes Adolescence-Onset FSGS

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ABSTRACT

Hereditary defects of coenzyme Q_{10} biosynthesis cause steroid-resistant nephrotic syndrome (SRNS) as part of multiorgan involvement but may also contribute to isolated SRNS. Here, we report 26 patients from 12 families with recessive mutations in *ADCK4*. Mutation detection rate was 1.9% among 534 consecutively screened cases. Patients with *ADCK4* mutations showed a largely renal-limited phenotype, with three subjects exhibiting occasional seizures, one subject exhibiting mild mental retardation, and one subject exhibiting retinitis pigmentosa. *ADCK4* nephropathy presented during adolescence (median age, 14.1 years) with nephrotic-range proteinuria in 44% of patients and advanced CKD in 46% of patients at time of diagnosis. Renal biopsy specimens uniformly showed FSGS. Whereas 47% and 36% of patients with mutations in *WT1* and *NPHS2*, respectively, progressed to ESRD before 10 years of age, ESRD occurred almost exclusively in the second decade of life in *ADCK4* nephropathy. However, CKD progressed much faster during adolescence in *ADCK4* than in *WT1* and *NPHS2* nephropathy, resulting in similar cumulative ESRD rates (>85% for each disorder) in the third decade of life. In conclusion, *ADCK4*-related glomerulopathy is an important novel differential diagnosis in adolescents with SRNS/FSGS and/or CKD of unknown origin.

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Mitochondrial cytopathies are clinically and genetically heterogeneous disorders. Although most mitochondriopathies involve multiple organ systems and often present with prominent neurologic and myopathic features in childhood, a few exhibit organ-selective phenotypes.[1] In the kidney, mitochondriopathies typically cause proximal tubulopathy[2]; however, glomerular dysfunction has been reported with mitochondrial DNA mutations in the $tRNA^{LEU}$ gene and coenzyme Q biosynthesis defects.[2–5]

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Coenzyme Q (ubiquinone; CoQ_{10}) is a component of the mitochondrial respiratory chain,[4] a potent lipophilic antioxidant, and a cofactor for mitochondrial dehydrogenases and in pyrimidine nucleoside biosynthesis. CoQ_{10} is synthesized ubiquitously through a multienzyme complex at the inner mitochondrial membrane. Mutations in several genes encoding enzymes of the CoQ_{10} biosynthetic pathway (*COQ2*, *COQ6*, and *PDSS2*) are associated with a glomerular phenotype. These have been collectively termed CoQ_{10} glomerulopathies.[2] Recently, recessive mutations in *ADCK4* (AarF Domain Containing Kinase-4) have been added to this list as a novel cause of steroid-resistant nephrotic syndrome (SRNS).[6] ADCK4 interacts with components of the CoQ_{10} biosynthesis pathway, and patients with *ADCK4* mutations have reduced cellular CoQ_{10} content.[6,7] The selective glomerular phenotype of patients with *ADCK4* mutations may be the result of relative enrichment of ADCK4 and lacking expression of the related protein ADCK3 in podocytes, whereas ADCK3 expression exceeds that of ADCK4 in most other body tissues.[6]

We identified a new patient cohort with *ADCK4* glomerulopathy among 534 consecutive SRNS cases. *ADCK4* mutations were found in ten patients (1.9%) from mostly consanguineous families. In five families the mutation was found in further affected siblings (Supplemental Figure 1: Families III–VII). Two additional families comprising nine affected subjects in whom *ADCK4* mutations were identified by genome-wide linkage analysis or exome sequencing (Supplemental Figure 1: Families I, II), yielding a total cohort of 26 patients. Mutational analysis revealed four novel sequence variants and three previously reported homozygous mutations, namely c.645delT, c.1199_1200dupA, and c.532C>T; p.(Arg178Trp) substitution.[6] The novel c.1339dupG variant was found in four apparently unrelated Kurdish families originating from a region in southeast Turkey, suggesting a founder effect. Bioinformatic information on the novel variants is given in Table 1 and the online supplement.

Table 1. Summary of bioinformatic analyses of the detected novel sequence variants

Novel variant	Residue change	Protein domain	MAF[a]	Conservation	Human Splicing Finder 3.0	Grantham difference score	PolyPhen score	SIFT score	Mutation taster prediction
c.293T>G	p.(Leu98Arg)	transmembrane (helical)	0 (not reported) 0.3%[b]	highly conserved, within conserved region	mutation in early exonic positions potentially breaking ESE site	102	1.0 probably damaging	0 damaging	disease causing
c.929C>T	p.(Pro310Leu)	kinase (ABC1 subdomain)	0 (not reported)	highly conserved	mutation in late exonic positions potentially breaking ESE site	98	1.0 probably damaging	0 damaging	disease causing
c.1493_1494CC>AA	p.(Ala498Glu)	–	0 (not reported)	low conservation	potential creation of exonic ESE site	93	0.173 benign	0 damaging	disease causing
c.1339dupG	p.(Glu447Glyfs10)	–	<1:10,000 0.3%[b]	highly conserved	potential activation of exonic cryptic acceptor site, or alteration of exonic ESE site, or creation of exonic ESS site	NA	NA	NA	disease causing

ESE, exonic splicing enhancer; ESS, exonic splicing silencer; NA, not applicable.
[a]MAF, minor allele frequency; estimation based on data of 2577 individual genomes cataloged by the 1000 Genomes Project; 6503 samples collected at NHLBI Exome Sequencing Project and data from 60,706 individuals aggregated by the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org); (accessed January 31, 2015).
[b]In-house allele frequency database representative for Turkish population (collection of 373 individual genomes; accessed October 22, 2014).

The phenotypic profile is summarized in Table 2. The disease first manifested in adolescence, typically with mild to moderate proteinuria with no or mild edema. However, advanced CKD was present in almost half of patients at time of diagnosis and progression to ESRD occurred in 22 of the 26 patients within a median of 9 (interquartile range 0–44) months from diagnosis. Hematuria was present at time of diagnosis in 25% of patients, including one case with a chief complaint of macroscopic hematuria accompanied by only trace proteinuria. FSGS was diagnosed in all biopsies, including two differentiated as collapsing and tip lesion subtypes.

Signs and symptoms compatible with neurologic dysfunction were reported in six patients (Supplemental Table 1). Mild mental retardation and agoraphobia were each present in one case and two siblings had primary nocturnal enuresis. Three patients developed electroencephalogram-confirmed seizures, including two while on dialysis. One subject was eventually diagnosed with hypertension-related reversible posterior encephalopathy whereas the other two require continued anticonvulsive therapy. One patient presented with retinitis pigmentosa. No histories of hearing problems, cardiomyopathy, muscle weakness, optical nerve atrophy, or hematologic or endocrinologic abnormalities were reported in any patient. Serum lactate was episodically elevated in 4 of 11 patients tested, and transient creatine kinase elevation was noted in two patients during episodes of AKI.

The clinical phenotype of *ADCK4*-related glomerulopathy was compared with the phenotypes of the two most common genetic podocytopathies, *i.e.*, *NPHS2*- and *WT1*-associated nephropathies (Figure 1, Table 2). Patients with *ADCK4*-related glomerulopathy were significantly older at time of diagnosis, with no cases manifesting before 5 years of age, and they presented with less severe proteinuria and less edema than *WT1*- or *NPHS2*-associated disease. Hypertension was less common than in *WT1* nephropathy. FSGS was the histopathologic diagnosis in all biopsied *ADCK4* cases, whereas diagnoses other than FSGS were commonly observed at time of diagnosis in *NPHS2* (Mesangioproliferative GN, Minimal change GN) and *WT1* nephropathy (diffuse mesangial sclerosis). In *ADCK4* patients, advanced CKD at time of diagnosis was more prevalent than in *NPHS2*. Of patients with *ADCK4* disease, 38.5% presented with CKD5, compared with 15.6% of *WT1* and 2.9% of *NPHS2* cases ($P<0.001$). Whereas 47% of *WT1* and 36% of *NPHS2* patients progressed to ESRD before reaching 10 years of age, ESRD occurred almost exclusively in the second decade of life in *ADCK4* nephropathy (Figure 1). However, CKD progression was much faster during adolescence in *ADCK4* than in *WT1* and *NPHS2* nephropathy, resulting in similar cumulative ESRD rates (>85%) for the three genetic forms of SRNS in the third decade of life. Neurologic deficits were more frequent in *ADCK4* disease. Renal and urinary tract malformations occurred almost exclusively in *WT1*. Other congenital anomalies, mostly heart structural defects, were anecdotally reported in all groups.

Table 2. Comparison of clinical characteristics at time of diagnosis and prospective kidney survival of patients with *ADCK4*-related SRNS versus patients with *NPHS2*- and *WT1*-related glomerulopathy from the PodoNet Registry[8]

	ADCK4 SRNS	*NPHS2* SRNS	*WT1* SRNS[d]
n	26	140	66
Age at first reported manifestation, years	14.1 (10.8–17.0)	3.4 (1.1–6.6)[d]	2.0 (0.7–5.4)[d]
Asymptomatic, incidental diagnosis	26.9%	22.9%	28.1%
Edema (none/mild/moderate/severe)	54/42/4/0%	48/17/16/19%	47/19/24/10%
Proteinuria (subnephrotic/nephrotic range)	57.1/43.9%	14.9/85.1%[d]	19.4/80.6%[c]
Hematuria	25.0%	44.0%	26.3%
Hypertension	30.8%	15.7%	41.5%[b]
CKD stage 3–5	46.1%[a]	13.6%[a,d]	23.4%[a,b]
including RTT:	26.9%[a]	2.9%[a,d]	15.6%[a]
Age at start of RRT, years	16.1 (13.7–18.0)[a]	12.9 (7.6–19.4)[a,d]	10.9 (2.3–17.0)[a,d]
Histopathological diagnosis			
FSGS/global glomerulosclerosis	61.5%	49.3%	45.0%
Diffuse mesangial sclerosis	0	0.7%	33.3%[d]
Mesangioproliferative GN	0	12.9%	4.5%
Minimal change GN	0	10.7%	1.5%
Other	0	5.0%	3.0%
No data/ not performed	38.5%	21.4%	13.7%
Neurologic abnormalities (seizures, NI, behavioral problems)	24.0%	5.0%[c]	6.1%b[b]
Congenital organ abnormalities	CAKUT 4.0% Other 8.0%	CAKUT 0% Other 5.7%	CAKUT 42.2%[d] Other 4.5%

Data are given as median (interquartile range) or percentage. Sixty-one of the patients with *WT1* mutations were previously described by Lipska *et al.* (2014)[9]

[a]Percentages given are relative to all observation with information on a specific variable.

[b]$P<0.05$.

[c]$P<0.01$.

[d]$P<0.001$.

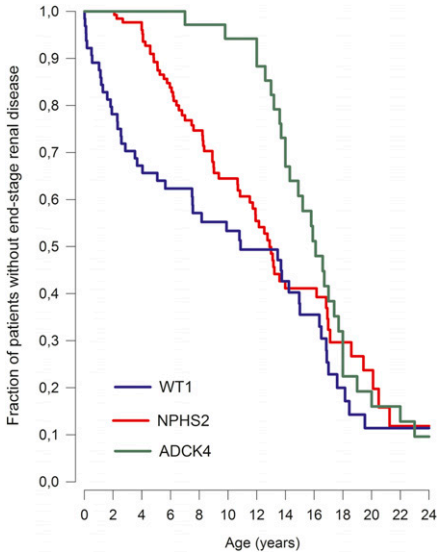

Figure 1. Age at attainment of ESRD by genetic cause of glomerulopathy. Thirty-five patients with *ADCK4* glomerulopathy (current series plus nine previously published cases[6]), 140 cases of *NPHS2*-associated SRNS and 66 cases of *WT1*-associated SRNS from PodoNet Registry.[8,9]

Immunosuppressive therapy was applied in 11 cases, of which only in two siblings an apparent partial initial response to oral steroids was reported. One patient progressed to ESRD at age 14 years, whereas the other is still on conservative therapy 8 years after diagnosis of SRNS and is currently on cyclosporin and angiotensin-converting enzyme inhibition, with persistent proteinuria of 2.5 g/m^2 per day. Two patients were diagnosed while still being asymptomatic with only minimal proteinuria and normal kidney function, thanks to the identification of *ADCK4* mutations in older siblings with established CKD. These subjects were started on CoQ_{10} supplementation soon after diagnosis and demonstrated a decrease of proteinuria by 50% and 80%, respectively, within 6 weeks of treatment (Figure 2, Supplemental Materials).

Our assembly and detailed phenotypic characterization of the largest *ADCK4* nephropathy cohort to date allowed us to demonstrate or corroborate several features that make *ADCK4* disease unique among the hereditary glomerulopathies in general and among those related to mitochondrial dysfunction in particular. In patients with mutations in *PDSS2*, *COQ2*, and *COQ6*, the other mitochondriopathy genes associated with SRNS, renal symptoms usually occur as part of a multisystemic disease complex encompassing progressive encephalopathy, ataxia, seizures, mental retardation, deafness, retinopathy, hypertrophic cardiomyopathy, and generalized myopathy.[1–5,10] By contrast, *ADCK4* disease typically manifests as an isolated nephropathy with only occasional extrarenal symptomatology. Combining our cohort with five previously published cases with available data on extrarenal involvement,[6] we oversee 30 patients from 17 families with detailed phenotypic information. Among these, 15 patients (50%) never showed any extrarenal system involvement. Three patients presented seizures (thereof two while on dialysis), and two patients each had mild mental retardation and behavioral problems. Two cases of goiter and single cases of retinitis pigmentosa and a lupus-like syndrome were reported. Occasionally observed transient mild elevations of lactate and creatine kinase during AKI are of questionable specificity and relevance.

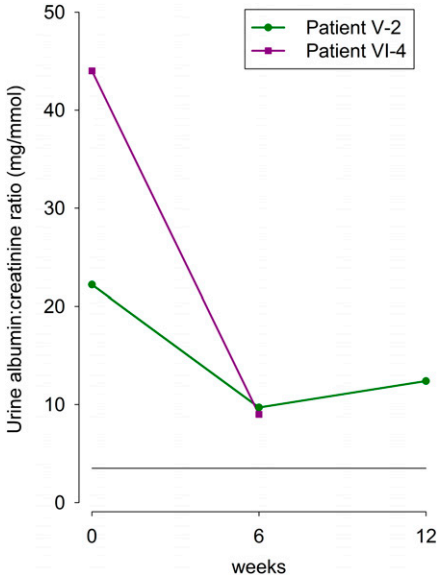

Figure 2. Changes in albuminuria after starting CoQ_{10} supplementation in patients with early-stage *ADCK4* glomerulopathy. Changes shown for two subjects detected in the asymptomatic early stage of the disease as a result of our study (further presented in Supplemental Material).

Hence, within the wide spectrum of mitochondrial disorders *ADCK4* mutations lead to the most selective glomerular involvement, possibly related to preferential enrichment of ADCK4 in podocytes. The cytosolic as well as mitochondrial localization of ADCK4 protein in podocytes has led to speculation that ADCK4 may exert additional functions other than CoQ_{10} biosynthesis.[6] Notwithstanding the preferential renal phenotype, patients diagnosed with *ADCK4* nephropathy should undergo systematic and repeated screening for subclinical extrarenal symptoms.

Our systematic screening of more than 500 prospective SRNS cases suggests that *ADCK4* nephropathy may be the third most common hereditary cause of SRNS, with a detection rate of one in 50 patients compared with one in eight for *NPHS2*[8] and one in 18 for *WT1*.[9] The renal phenotype of *ADCK4* disease is characterized by an insidious onset at adolescence with mild to moderate proteinuria and absence of relevant edema in the majority of cases. As a consequence of the oligosymptomatic early course, advanced CKD is often present at the time of diagnosis. The comparison of renal survival of patients with *ADCK4*, *WT1*, and *NPHS2* glomerulopathies respectively demonstrates the unusual evolution of renal function in the mitochondriopathy, with almost all patients progressing to ESRD between 12 and 23 years of age. Hence, at the current stage of knowledge SRNS progressing toward ESRD in the first decade of life almost rules out *ADCK4* disease, whereas *ADCK4* nephropathy is an important differential diagnosis to consider in cases of adolescent-onset multidrug-resistant proteinuria with FSGS on biopsy. In this group, where genetic causes are found in less than 10% of cases by conventional screening,[11,12] mutations in *ADCK4* may be as common as those in *NPHS2* and *WT1*. Of course, the experience derived from the first two disease cohorts comprising patients from 20 families with 15 different mutations is still limited.

It remains to be seen whether the suggested detection rate will be confirmed and whether the uniform disease pattern will diversify with the identification of more patients and mutations.

The CoQ_{10} glomerulopathies represent the first hereditary forms of SRNS for which a causative molecular therapy is potentially available. Oral CoQ_{10} supplementation may reverse proteinuria and stabilize kidney function if applied early in the disease course.[5,6,10,13] The commonly late diagnosis of *ADCK4* disease so far has precluded efficient therapy in most affected patients. This situation may change in the near future with earlier diagnosis thanks to increased awareness of the disease entity, inclusion of the mitochondrial genes in routinely performed next generation sequencing (NGS) panel screening, and proteinuria screening of asymptomatic siblings of affected patients as accomplished in two children in this report. Both subjects indeed demonstrated a significant decrease of proteinuria on CoQ_{10} supplementation, raising hopes that timely treatment may preserve podocyte and kidney function in children with *ADCK4* nephropathy.

Based on the preliminary evidence presented here, we propose to perform *ADCK4* sequencing, ideally as part of NGS panel screening, in all patients with adolescent-onset proteinuric kidney disease in whom autoimmune etiologies have been ruled out on clinical and biochemical grounds. Genetic screening should be prioritized over kidney biopsy, particularly in cases of familial disease occurrence or parental consanguinity.

In conclusion, *ADCK4* glomerulopathy is a novel cause of adolescent-onset SRNS caused by defective CoQ_{10} biosynthesis in podocytes. This recessive Mendelian disease may present with signs and symptoms of systemic mitochondrial dysfunction, but more often manifests as isolated FSGS. Despite the late clinical manifestation, rapid progression to end-stage renal disease is common. Early diagnosis will help to identify children at early disease stages who are eligible for oral CoQ_{10} supplementation.

CONCISE METHODS

ADCK4 screening was performed in 534 consecutive SRNS patients from the PodoNet Registry and in-house biobanks at Necker Hospital in Paris, France, the Hacettepe University Nephrogenetics Laboratory, Ankara, Turkey, and the Molecular Genetics Unit at Bioscientia, Ingelheim, Germany. Clinical information was available for 349 patients, including 233 unrelated patients negative for mutations in the first-line SRNS-associated genes (*NPHS2*, exons 8–9 of *WT1*) and 116 not previously tested individuals.

The PodoNet, Necker, and Bioscientia cohorts underwent high-throughput sequencing using custom-designed multi-gene NGS panels for FSGS and related glomerulopathies. Sequencing was performed using the MiSeq/HiSeq platform (Illumina, San Diego, CA). All findings were verified by Sanger sequencing, which was also used to test eligible family members.

Comparator cohorts with SRNS related to mutations in *NPHS2* (n=140) or *WT1* (n=66) were extracted from the PodoNet Registry.[8,9]

Whole-genome linkage analysis using 250K single nucleotide polymorphism array (Affymetrix, Santa Clara, CA) followed by homozygosity mapping using VIGENOS software was performed in two index families (Supplemental Figure 1: Families I and II). Illumina TruSeq Exome Enrichment Kit was used for paired-end whole exome sequencing performed on an Illumina HiSeq 2000 sequencing system (Illumina, San Diego, CA).

Detailed clinical information on renal and extrarenal symptoms was obtained on all *ADCK4* patients by way of a standardized questionnaire. The patient-level data are given in Supplemental Table 1. Statistical analyses were performed using the STATISTICA 9.1 (StatSoft; Tulsa, OK) data analysis software system.

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DISCLOSURES

None.

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