Podocyte-associated gene mutation screening in a heterogeneous cohort of patients with sporadic focal segmental glomerulosclerosis

Louis-Philippe Laurin1,*, Mei Lu2,*, Amy K. Mottl1, Elizabeth R. Blyth1, Caroline J. Poulton1
and Karen E. Weck2

1Division of Nephrology and Hypertension, UNC Kidney Center, University of North Carolina, Chapel Hill, NC, USA and 2Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC, USA

Correspondence and offprint requests to: Karen E. Weck; E-mail: kweck@unc.edu

*These authors contributed equally to this work.

ABSTRACT

Background. The utility of genetic testing in sporadic focal segmental glomerulosclerosis (FSGS) is unclear. We sought to determine the frequency of podocyte-related gene mutations in a heterogeneous population of adults and children with biopsy-proven FSGS.

Methods. The prevalence of pathogenic mutations in five genes (NPHS2, TRPC6, ACTN4, INF2 and PLCE1) and of APOL1 risk alleles (G1 and G2) was ascertained in children and adults diagnosed between 1984 and 2011 with FSGS by renal biopsy. Clinical data were extracted from medical records.

Results. A total of 65 patients (28 children, 37 adults) with sporadic FSGS were identified (34 females, 31 males), with a mean age of 25 ± 16 years (range from 3 to 62 years). The majority of patients were African American (39 African American, 21 White and 2 Hispanic). We identified biallelic pathogenic NPHS2 mutations in 2 of 28 (7.1%) children, both of whom were of non-Hispanic Caucasian background. A homozygous NPHS2 p.R138Q/p.R138Q mutation was detected in a 5-year-old Caucasian female. Two compound heterozygous NPHS2 mutations p.R138Q/p.R229Q were identified in a 7-year-old Caucasian male patient. One novel, potentially pathogenic non-synonymous variant in INF2 was identified in an African American patient. The proportion of African Americans with two APOL1 risk alleles was 69.2%.

Conclusions. This study delineates a role for genetic testing for NPHS2 in children with biopsy-proven sporadic FSGS. Further studies which specify clinical and pathological details of patients will help further define whether there are specific populations that warrant systematic testing of other podocyte-related genes in sporadic FSGS.

Keywords: APOL1, genetic screening, podocyte-related gene mutations, sporadic FSGS, steroid-resistant nephrotic syndrome

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is the most common cause of nephrotic syndrome in adults and a major cause of end-stage kidney disease (ESKD) in both children and adults [1, 2]. FSGS can be described as a pattern of glomerular injury that encompasses five ‘variants’ with distinct clinical presentations and renal outcomes [3, 4]. FSGS has been recognized as a common cause of steroid-resistant nephrotic syndrome (SRNS), especially in the pediatric population where the prevalence of this clinical entity has increased to 60–70% of SRNS [2, 5].

Recent discovery of several podocyte-related gene mutations unveils FSGS as a quintessential podocyte disease or ‘podocytopathy’ [2]. Indeed, causative podocyte-associated gene mutations have been identified in various populations of patients with SRNS [6]. The most prevalent podocyte-related gene mutations associated with non-syndromic SRNS involve NPHS1, NPHS2 and PLCE1, which are of autosomal recessive inheritance, and TRPC6, ACTN4 and INF2, which present with autosomal dominant transmission [6].
The prevalence of mutations in sporadic FSGS has been hard to infer from the literature given the significant overlap between familial and sporadic cases, differing inclusion criteria (SRNS versus biopsy-confirmed FSGS) and inconsistent racial composition of studied populations. Hence, minimal data exist on the prevalence of causal mutations in podocyte-associated genes in biopsy-proven FSGS in a population with assorted ethnicities and a wide age spectrum. Furthermore, publications portraying the main causal podocyte-related mutations in African Americans are scarce, most notably in children.

Thus, in the present study, we sought to determine the prevalence of genetic mutation in NPHS2, TRPC6, ACTN4, INF2 and PLCE1, and APOL1 risk-allele frequencies among patients of varying age and ethnicity with sporadic FSGS.

**Materials and Methods**

**Study design and population**

Patients with FSGS diagnosed between 1984 and 2011 and enrolled into the Glomerular Disease Collaborative Network were eligible for this incident disease cohort study. All information was compiled in a computerized registry.

Subjects with definitive pathologic findings of FSGS on kidney biopsy based on at least five glomeruli assessed by light microscopy were included in this cohort. Patients with a known secondary cause of FSGS, such as human immunodeficiency virus (HIV), hepatitis B and C, intravenous drug use, sickle-cell disease, single kidney, reflux nephropathy and other types of glomerulonephritis, were excluded. Renal biopsies from kidney transplants were also excluded from analysis. The participants were ascertained via our general pediatric and adult nephrology clinics, and participants in the FSGS clinical trial. Study participants provided a written, informed consent. This study was reviewed and approved by the University of North Carolina’s Institutional Review Board in agreement with the Declaration of Helsinki.

**Clinical data and definitions**

Clinical and laboratory variables were obtained by retrospective review of medical records from renal biopsy to the last available follow-up visit and/or initiation of renal replacement therapy. Age considered for analysis was age at the time of renal biopsy.

Kidney biopsy samples were evaluated by the University of North Carolina’s Nephropathology Laboratory. Biopsy findings were recorded per description on the renal biopsy report. FSGS variants were ascertained according to the Columbia FSGS classification system and documented as stated on the official report [3]. Three FSGS variants were considered for the purpose of this study: not otherwise specified (NOS), tip lesion and collapsing. NOS and perihilar FSGS cases were aggregated under the category ‘other FSGS’ and collapsing FSGS included cases with cellular FSGS.

Complete remission was defined as a reduction in proteinuria to ≤0.3 g/24 h (or 0.3 g/g on urinary protein-to-creatinine ratio) with stable serum creatinine (not >25% increase in serum level between biopsy diagnosis and proteinuria quantification). Partial remission was defined as a reduction in proteinuria of ≥50% with proteinuria excretion <3.5 g/24 h (or 2.0 g/g on urinary protein-to-creatinine ratio) and >0.3 g/24 h or 0.3 g/g with stable renal function. ESKD was defined as initiation of renal replacement therapy either by chronic dialysis or kidney transplantation. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula for adults and the Schwartz formula for children [7, 8].

**Mutational analyses**

Mutations were ascertained by Sanger DNA sequencing of selected genomic regions in which pathogenic mutations have been described for ACTN4 (exons 2, 7 and 8), INF2 (exons 2 and 4) and PLCE1 (exon 2, 3, 10, 14, 18, 21 and 25) and for the entire coding region and flanking intronic regions of NPHS2 and TRPC6. Sanger sequencing analysis was used to determine the genotype for the APOL1 G1 (rs73885319, rs60910145) and G2 (rs71785313) risk alleles associated with increased risk of kidney disease among African Americans. Mutations in NPHS1 were not evaluated as no patients with biopsy-proven FSGS were younger than age 1.

Genomic deoxyribonucleic acid (DNA) was isolated from peripheral blood samples using a QIAamp DNA mini kit (Qiagen, Hilden, Germany) or on an automated DNA extraction MagNA Pure System (Roche Diagnostics, Indianapolis, IN). Sanger dideoxy DNA sequencing analysis was performed using oligonucleotide DNA primers specific for the relevant genomic regions. An M13 phage tag was added to the 5’ end of each primer for sequencing purposes. Each PCR reaction contained 0.25 μM forward and reverse primers and 20 ng of DNA template. Due to high GC content in some exons, 10% dimethyl sulfoxide was included in those reactions. PCR products were subjected to DNA sequencing using the Sanger dye-terminator method on a 3130xl genetic analyzer (Applied Biosystems, Carlsbad, CA). Sequencing analysis was performed using Seqscape v2.6 (Applied Biosystems, Carlsbad, CA).

**Statistical analyses**

Continuous variables with normal distribution are expressed as mean ± standard deviation. Non-parametric variables are expressed as median [interquartile range (IQR)]. Categorical data are expressed as proportions. Statistical analyses were performed using SPSS 16.0 (IBM Corporation, Armonk, NY) software. L.-P.L. analyzed the dataset.

**Results**

**Patient characteristics**

A total of 65 patients were identified (34 females, 31 males), with a mean age of 25 ± 16 years (range from 3 to 62 years) (Table 1). The majority (63%) of patients were African American (39 African American, 21 White and 2 Hispanic). Nephrotic syndrome was the reason for first clinic contact in 41.5% of patients. No documented family history of primary nephrotic syndrome or podocytopathy was present in any of the subjects.
The first patient (NPHS2 p.R138Q homozygous) was diagnosed at the age of 5 with FSGS NOS by renal biopsy. She had developed severe nephrotic syndrome with serum albumin and proteinuria of, respectively, 16 g/L and 22.0 g/g at onset. Her baseline serum creatinine was 18 μmol/L. She was exposed to renal replacement therapy at last follow-up.

Four of 39 patients with available data had a history of proteinuria in the family. The median eGFR was 78 mL/min/1.73 m² (IQR: 50–100 mL/min/1.73 m²) in children. The mean eGFR was 69 ± 37 mL/min/1.73 m² in adults. Thirty-nine patients (60%) were exposed to calcineurin inhibitor therapy, with an overall remission rate of 60%. The median follow-up time was 45 months (IQR: 26–75 months). Sixteen patients (25%) were on renal replacement therapy at last follow-up.

Pathogenic mutations and their phenotypes

Two Caucasian patients with childhood-onset FSGS tested positive for known pathogenic NPHS2 mutations (Table 2 and Figure 1). A homozygous NPHS2 p.R138Q/p.R138Q mutation was detected in a 5-year-old Caucasian female. Two compound heterozygous NPHS2 mutations p.R138Q/p.R229Q were identified in a 7-year-old Caucasian male patient. There was no clear family history of kidney disease in either case. No known pathogenic mutations in TRPC6, ACTN4, INF2 or PLCE1 were found in this FSGS cohort.

The second patient (NPHS2 p.R138Q homozygous) was diagnosed at the age of 7 with FSGS NOS at the age of 7. He presented with significant proteinuria, quantitated to 2.3 g/g, and concomitant both steroid and calcineurin inhibitor therapies throughout the course of her renal disease with no documented response to therapy. The patient was started on renal replacement therapy 52 months after her initial FSGS diagnosis.

FIGURE 1: Racial distribution among different age groups. Documented cases with NPHS2 mutations denoted by black arrows.
mild hypoalbuminemia of 26 g/L. His baseline eGFR was 116 mL/min/1.73 m². The patient was treated with steroids alone, and his proteinuria went down to 1.3 g/g at last follow-up. He was subsequently transitioned to an angiotensin-converting-enzyme inhibitor with preservation of renal function and no need for renal replacement therapy. His serum creatinine after 46 months of follow-up was 35 μmol/L.

**APOL1 risk-allele frequencies**

A total of 34 patients (52.3%) carried one or two APOL1 risk alleles (Table 3). APOL1 G1 and/or G2 risk alleles were found in 31 of 39 (79.5%) African American patients, with 27 of 39 (69.2%) African Americans carrying 2 APOL1 risk alleles. Allele frequencies in African American patients were 69.2% for G1 and 35.9% for G2.

Among Caucasian patients, 1 of 21 (4.8%) carried APOL1 risk alleles: 1 FSGS NOS case was a G1/G2 compound heterozygote.

**Mutations of unknown significance**

One 18-year-old Caucasian male with late-onset FSGS was identified with two heterozygous NPHS2 mutations p.R229Q/p.R10T. His initial presentation was consistent with tip lesion FSGS with severe edema, 6.7 g per day of proteinuria and serum albumin of 24 g/L. His baseline eGFR was 124 mL/min/1.73 m². The patient did not respond to steroids initially. He was subsequently converted to cyclosporine. The patient went into complete remission with calcineurin inhibitor therapy and remained in remission >10 years after stopping all immunosuppressive agents.

Additionally, we identified several non-synonymous genetic variants of unknown significance (Table 4). A novel, potentially deleterious non-synonymous variant in the INF2 gene c.436C>A, p.L146I was identified in an African American male with late-onset FSGS and no family history of kidney disease. In addition to the patient described above, a heterozygous NPHS2 p.R10T mutation was identified in a second patient in the absence of any other NPHS2 variant. Three individuals had single non-synonymous variants in PLCE1 without any second variant identified. Two subjects with a PLCE1 variant had a history of proteinuria in the family.

**DISCUSSION**

This study is among the first to take a methodical approach for testing multiple podocyte-related genes in a heterogeneous cohort of patients with biopsy-proven primary FSGS. Our findings suggest that in patients with FSGS without a family history of kidney disease, there is a clinically significant yield to genetic testing for NPHS2 in children. We identified biallelic pathogenic NPHS2 mutations consistent with autosomal recessive SRNS in 2 of 7 Caucasian children (28.6%) with early-onset, biopsy-proven FSGS. The prevalence of NPHS2 mutations in Caucasian children with sporadic FSGS reported in previous studies ranges between 0 and 9% (Table 5). Given the limited number of Caucasian children in our study, it remains to be established whether this might relate to a true difference in the populations under study.

NPHS2 mutations were amongst the first mutations identified in children with a family history of SRNS with FSGS [30]. In non-familial cases, the reported prevalence of NPHS2 mutations has been variable, ranging from 0 to 9%, which reflects disparate definitions of SRNS and varying cohort age of disease onset and ethnicity [10, 13–17, 24, 31]. There is a paucity of data on the prevalence of NPHS2 mutations in sporadic FSGS in African American children, with a published cohort of 13 individuals reporting no causative mutations [15]. Moreover, NPHS2 pathogenic mutations have never been reported in adult African American patients and are described infrequently in adult subjects of European ancestry, with the highest reported prevalence being 5.0% from a cohort in Spain [10, 22–26]. The low prevalence of Caucasian adults in our cohort may explain our lack of positive findings; however, further studies are necessary to elucidate the indications for NPHS2 testing in adults from varying ethnic backgrounds.

Of the two children with definitive NPHS2 mutations, three of the four alleles were the p.R138Q mutation, which has been reported to account for >30% of mutant NPHS2 alleles in Caucasians [32, 33]. It has been associated with very early-onset, severe SRNS and has been shown to be a null mutation leading to retention of podocin in the endoplasmic reticulum and failure to recruit nephrin to lipid rafts [13, 34–36]. The finding of homozygosity for NPHS2 p.R138Q in a child with severe, early-onset SRNS is consistent with previous reports of this mutation.

The fourth known deleterious allele we identified was the controversial NPHS2 p.R229Q single nucleotide polymorphism (SNP), prevalent in 5% of Caucasians, but reported to be associated with late-onset SRNS when in compound heterozygosity with another pathogenic NPHS2 mutation [34, 36, 37]. Interestingly, we identified compound heterozygosity for the severe, early-onset p.R138Q and the reported mild, late-

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Table 3. **APOL1 risk alleles by ethnicity**

<table>
<thead>
<tr>
<th>Number of APOL1 risk alleles</th>
<th>Ethnicity</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>African</td>
<td>American</td>
<td>Hispanic</td>
</tr>
<tr>
<td>0</td>
<td>20</td>
<td>8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1 (G1 or G2)</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 (G1 or G2 homozygote; G1/G2 heterozygote)</td>
<td>1</td>
<td>27</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. **Non-synonymous variants of unknown significance detected among 65 patients with FSGS**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>PolyPhen-2 prediction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPHS2</td>
<td>c.29G&gt;C, p.R10T</td>
<td>Likely benign</td>
<td>2/65</td>
</tr>
<tr>
<td>INF2</td>
<td>c.436C&gt;A, p.L146I</td>
<td>Probably damaging</td>
<td>1/65</td>
</tr>
<tr>
<td>PLCE1</td>
<td>c.1400C&gt;T, p.T467I</td>
<td>Probably damaging</td>
<td>1/65</td>
</tr>
<tr>
<td></td>
<td>c.1495C&gt;T, p.R499C</td>
<td>Probably damaging</td>
<td>1/65</td>
</tr>
<tr>
<td></td>
<td>c.1729G&gt;A, p.A577T</td>
<td>Possibly damaging</td>
<td>1/65</td>
</tr>
</tbody>
</table>

*Phenotype prediction was performed using PolyPhen-2 in silico prediction algorithm.
onset p.R229Q mutation in a 7-year-old child with later onset, milder disease than is typically seen in individuals with the p.R138Q mutation. Although some have advocated screening for NPHS2 p.R229Q in adult-onset cases in order to identify patients who may have a second pathogenic mutation, we found only 1 of 40 adult-onset patients with this variant in an 18-year-old Caucasian. Moreover, this individual was negative for an additional known pathogenic NPHS2 mutation, but had a p.R10T variant of unknown clinical significance [32, 38].

The p.R10T variant is a non-synonymous (missense) variant of uncertain pathogenic significance. In silico prediction algorithms sorting intolerant from tolerant (SIFT) and polymorphism phenotyping 2 (PolyPhen-2) have predicted it to be tolerated or benign, but it has not been well characterized functionally. In addition, a heterozygous NPHS2 p.R10T mutation was identified in a second patient in the absence of any other NPHS2 variant, raising the possibility that the p.R10T may be a common polymorphism.
We did not identify any definitive pathogenic mutations in podocyte genes associated with autosomal dominant transmission in either children or adults with sporadic FSGS. We did, however, find a novel, potentially pathogenic, non-synonymous variant in the INF2 gene c.436C>T, p.L146I in an African American patient with adult-onset FSGS. PolyPhen-2 predicts this variant to be probably damaging. However, the prediction accuracy of in silico prediction programs such as PolyPhen-2, SIFT, etc. is <85% [39–41]. These programs demonstrate greater sensitivity than specificity and tend to overcall the pathogenicity of non-synonymous missense variants [39–41]. Thus, caution should be taken in using such in silico analyses to predict the pathogenicity of novel missense variants. In addition, although this variant has not been reported in previous analyses, common polymorphisms in African Americans are not as well characterized as in Caucasians. Thus, variants that appear to be novel may be common ethnicity-specific variants that have not been well characterized yet. The possibility exists that this INF2 mutation may be associated with autosomal dominant FSGS, but we remain cautious in our interpretation given the lack of convincing data at this time.

Hence, our results suggest that testing for autosomal dominant genes in individuals without a documented family history is of limited clinical utility. This is in contrast to other studies of TRPC6 in sporadic SRNS, which have documented detrimental mutations in both adult and childhood-onset disease [10, 17, 22]. Our results challenge other studies, which have advocated for systematic genetic testing in both adults and children with SRNS and an absence of a family history of kidney disease [10]. Possible explanations for this distinction may be due to our approach in targeting the specific phenotype of biopsy-proven FSGS in the absence of a family history, the ethnic heterogeneity of our cohort which was >50% African American, and the small number of patients in our study.

Three individuals had single, non-synonymous variants of unknown significance in PLCE1 without any second variant identified, which is not consistent with podocytopathy. Although it is possible that the identified variants are deleterious, PLCE1 is of autosomal recessive inheritance and thus the presence of a single variant is insufficient to cause late-onset FSGS. Of note is that the lack of prevalent pathogenic PLCE1 mutations in our cohort of FSGS patients is consistent with its involvement primarily in diffuse mesangial sclerosis.

Our findings are consistent with previous reports denoting an enriched incidence of APOL1 G1 and G2 risk alleles in the African American population with FSGS [42, 43]. The G1 and G2 SNPs are common variants in the African American population, with ~58% of African Americans carrying at least one risk allele and ~13% carrying two risk alleles in one large published study [43]. Consistent with previous reports, the incidence of the G1 and G2 risk alleles in African Americans with FSGS in our cohort was enriched over the general population incidence, with 79.5% carrying at least one risk allele and 69.2% carrying two risk alleles. Interestingly, 4.8% of Caucasians in our FSGS cohort carried two APOL1 risk alleles, although the G1 and G2 risk alleles are reportedly very rare in the Caucasian population (minor allele frequencies of <0.1%) [43, 44]. However, with only one Caucasian with the risk alleles, we cannot make any conclusions about the frequency of these alleles in Caucasians with FSGS. We also cannot rule out the possibility of inaccurate self-reporting of ethnicity as it is often based on skin color alone. Thus, our data are consistent with an association between the presence of APOL1 risk alleles and the development of FSGS; however, APOL1 is not associated with Mendelian inheritance of FSGS as with the other genes interrogated in this study, and other factors likely play a role in the development of FSGS in this population.

Variations in APOL1 have been recognized as having a role in the increased risk of kidney disease in African Americans with FSGS, hypertension-related kidney disease and HIV-associated nephropathy [42, 45, 46]. Although the pathogenesis is not well understood, localization of apolipoprotein-1 within smooth muscle cells in medium-sized arteries and arterioles in patients with FSGS or HIV-related nephropathy suggests that APOL1 variants may contribute to kidney disease progression through arterial wall damage and vascular dysfunction [47]. An association between APOL1 risk alleles and systemic lupus erythematosus-associated collapsing FSGS has been described recently, but implications of carrying APOL1 risk variants in idiopathic collapsing FSGS remain undefined [48]. Interestingly, 9 of 10 (90%) African American patients with collapsing FSGS in our cohort were found to have at least one risk allele for APOL1. Whether the presence of APOL1 risk alleles in collapsing FSGS confers a worse renal prognosis remains, however, unresolved.

There are limitations to our study which should be considered when interpreting the data. We did not test for mutations in genes that have historically been associated with specific phenotypes distinct from FSGS. Testing for WT1 is highest yield in children with abnormalities of external genitalia. At the time of the design of the present study, NPHS1 was thought to be relevant to congenital nephrotic syndrome which was an exclusion criterion and CD2AP is extraordinarily rare. Hence, it is possible that we may have missed mutations in these untested podocyte genes. In contrast, a recent study from McCarthy et al. [49] systematically screened 24 genes associated with SRNS using next generation sequencing in 36 children with congenital nephrotic syndrome or primary steroid resistance. Such an approach is not necessarily applicable to our population, in which half of the subjects were adult, and the renal pathology diagnosis was homogeneously FSGS.

The strength of our study lies in the heterogeneity of the population, the large number of African Americans, specific inclusion criteria and detailed clinical data. Much confusion surrounds the current state of knowledge with regard to the genotype–phenotype correlation of podocytopathies due to vague or absent clinical information in the literature. This study highlights the importance of providing detailed clinical phenotypic information when communicating causative or associated genetic variations or mutations. Precise phenotyping of which population(s) should be screened for specific mutations may make it possible to avoid unnecessary use of immunosuppressive agents [50].

In conclusion, genetic testing will become increasingly important to the care of patients with sporadic podocytopathies. However, the current state of knowledge does not support
widespread testing in all individuals with proteinuria. In the setting of a family history of unexplained kidney disease, there is clearly a role for genetic testing, targeting genes based upon the age at disease onset and mode of transmission. At this point in time, genetic testing in sporadic FSGS is clearly indicated for NPHS2 in children. Further studies that specify clinical and pathological details of patients will help further delineate whether there are other specific populations that warrant systematic testing of podocyte-related genes.

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CONFLICT OF INTEREST

The authors declare no competing financial interests. The results presented here have not been published previously in whole or in part, except in abstract form.


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The association between glomerular filtration rate and left ventricular function in two independent community-based cohorts of elderly

Elisabet Nerpin1,2, Erik Ingelsson3, Ulf Risérus4, Johan Sundström5, Bertil Andren5, Elisabeth Jobs1,2, Anders Larsson5, Lind Lars5 and Johan Ärnlöv1,2

1Department of Public Health and Caring Sciences/Geriatrics, Uppsala Science Park, Uppsala, Sweden, 2Department of Health and Social Sciences, Högskolan Dalarna, Falun, Sweden, 3Department of Medical Sciences, Molecular Epidemiology and Science for Life Laboratory, Uppsala University, Uppsala, Sweden, 4Department of Public Health and Caring Sciences/Section of Clinical Nutrition and Metabolism, Uppsala Science Park, Uppsala, Sweden and 5Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Correspondence and offprint requests to: Elisabet Nerpin; E-mail: ene@du.se

ABSTRACT

Background. The cardiorenal syndrome, the detrimental bi-directional interplay between symptomatic heart failure and chronic kidney disease, is a major clinical challenge. Nonetheless, it is unknown if this interplay begins already at an asymptomatic stage. Therefore we investigated whether the glomerular filtration rate (GFR) is associated with left ventricular function in participants free from clinical heart failure and with a left ventricular ejection fraction (LVEF) >40% and with pre-specified sub-group analyses in individuals with a GFR >60 mL/min/m².

Methods. Two independent community-based cohorts were used; the Prospective Investigation of the Vasculature in Uppsala (PIVUS) and the Uppsala-Örebro Study on Aging (UOSA).

Results. Two independent community-based cohorts were used; the Prospective Investigation of the Vasculature in Uppsala (PIVUS) and the Uppsala-Örebro Study on Aging (UOSA).

Conclusions. The results support the development of clinical guidelines and public health interventions in the early stages of heart failure and chronic kidney disease that are based on a thorough understanding of the underlying pathomechanisms.