Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management

Agnieszka Bierzynska[1], Hugh J. McCarthy[1], Katrina Soderquest[2], Ethan S. Sen[1], Elizabeth Colby[1], Wen Y. Ding[1], Marwa M. Nabhan[3], Larissa Kerecuk[4], Shivram Hegde[5], David Hughes[6], Stephen Marks[7], Sally Feather[8], Caroline Jones[9], Nicholas J.A. Webb[10], Milos Ognjanovic[11], Martin Christian[12], Rodney D. Gilbert[13], Manish D. Sinha[14], Graham M. Lord[2], Michael Simpson[15], Ania B. Koziell[2], Gavin I. Welsh[1] and Moin A. Saleem[1]

[1]Bristol Renal and Children's Renal Unit, School of Clinical Sciences, University of Bristol, UK; [2]Division of Transplantation Immunology and Mucosal Biology, Department of Experimental Immunobiology, Faculty of Life Sciences and Medicine, King's College London, London, UK; [3]Egyptian group for orphan renal diseases (EGORD), Department of paediatrics, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt; [4]Birmingham Children's Hospital, Birmingham, UK; [5]University Hospital of Wales, Cardiff, UK; [6]Royal Hospital for Children, Glasgow, UK; [7]Great Ormond Street Hospital, London, UK; [8]St James's University Hospital, Leeds, UK; [9]Alder Hey Children's Hospital, Liverpool, UK; [10]Department of Paediatric Nephrology and NIHR/Wellcome Trust Clinical Research Facility, University of Manchester, Manchester Academic Health Science Centre, Royal Manchester Children's Hospital, Manchester, UK; [11]Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK; [12]Nottingham Children's Hospital at the QMC, UK; [13]Southampton Children's Hospital and University of Southampton School of Medicine, Southampton, UK; [14]Guy's and St. Thomas' Hospital, London, UK; and [15]Division of Genetics and Molecular Medicine, Faculty of Life Sciences and Medicine, King's College London, London, UK

Steroid Resistant Nephrotic Syndrome (SRNS) in children and young adults has differing etiologies with monogenic disease accounting for 2.9–30% in selected series. Using whole exome sequencing we sought to stratify a national population of children with SRNS into monogenic and non-monogenic forms, and further define those groups by detailed phenotypic analysis. Pediatric patients with SRNS were identified via a national United Kingdom Renal Registry. Whole exome sequencing was performed on 187 patients, of which 12% have a positive family history with a focus on the 53 genes currently known to be associated with nephrotic syndrome. Genetic findings were correlated with individual case disease characteristics. Disease causing variants were detected in 26.2% of patients. Most often this occurred in the three most common SRNS-associated genes: *NPHS1*, *NPHS2*, and *WT1* but also in 14 other genes. The genotype did not always correlate with expected phenotype since mutations in *OCRL*, *COL4A3*, and *DGKE* associated with specific syndromes were detected in patients with isolated renal disease. Analysis by primary/presumed compared with secondary steroid resistance found 30.8% monogenic disease in primary compared with none in secondary SRNS permitting further mechanistic stratification. Genetic SRNS progressed faster to end stage renal failure, with no documented disease recurrence post-transplantation within this cohort. Primary steroid resistance in which no gene mutation was identified had a 47.8% risk of recurrence. In this unbiased pediatric population, whole exome sequencing allowed screening of all current candidate genes. Thus, deep phenotyping combined with whole exome sequencing is an effective tool for early identification of SRNS etiology, yielding an evidence-based algorithm for clinical management.

Kidney International (2016) ■, ■–■; http://dx.doi.org/10.1016/j.kint.2016.10.013

KEYWORDS: cytoskeleton; focal segmental glomerulosclerosis; nephrotic syndrome; pediatric nephrology; podocyte; proteinuria

Nephrotic syndrome is a heterogeneous entity only recently divided into mechanistic categories. Although population analyses have been limited in pediatric cohorts,[1–3] idiopathic nephrotic syndrome (INS) has an estimated incidence of approximately 2 to 5 per 100,000 children per year depending on ethnic background.[2] INS is currently classified into steroid sensitive (SSNS) or steroid resistant (SRNS), with at least 2.9% to 30% of SRNS cases (in series variably enriched for consanguineous disease or other phenotypes) now known to have an underlying Mendelian, genetic cause. A challenging subset of cases, considered to be immunologically mediated and caused by an as yet unidentified circulating factor(s) can present as secondary SRNS after initial steroid sensitivity.[4] The most dramatic evidence of the presence of a circulating factor is rapid recurrence of nephrotic disease soon after kidney transplantation in 40% to 60% of graft recipients with SRNS.

Correspondence: *Moin A. Saleem, University of Bristol, Children's Renal Unit and Bristol Renal, Dorothy Hodgkin Building, Whitson Street, Bristol BS1 3NY, United Kingdom. E-mail: M.Saleem@bristol.ac.uk*

Received 11 June 2016; revised 8 September 2016; accepted 6 October 2016

Table 1 | Fifty-three genes associated with steroid-resistant nephrotic syndrome (SRNS) of congenital, childhood, or adult onset[5–11]

Gene	Inheritance	Accession #	Disease
ACTN4[*]	AD	NM_004924	Familial and sporadic SRNS (usually adult)
ADCK4[*]	AR	NM_024876	SRNS
ALG1	AR	NM_019109	Congenital disorder of glycosylation
ANLN	AD	NM_018685	FSGS (mainly adult)
ARHGAP24	AD	NM_001025616	FSGS
ARHGDIA	AR	NM_001185078	CNS
CD151	AR	NM_004357	NS, pretibial bullous skin lesions, neurosensory deafness, bilateral lacrimal duct stenosis, nail dystrophy, and thalassemia minor
CD2AP	AD/AR	NM_012120	FSGS/SRNS
CFH	AR	NM_000186	MPGN type II + NS
COL4A3[*]	AR	NM_000091	Alport's disease/FSGS
COL4A4	AR	NM_000092	Alport's disease/FSGS
COL4A5[*]	X-linked AR	NM_000495	Alport's disease/FSGS
COQ2	AR	NM_015697	Mitochondrial disease/isolated nephropathy
COQ6	AR	NM_182476	NS ± sensorineural deafness; DMS
CRB2[*]	AR	NM_173689	SRNS
CUBN	AR	NM_001081	Intermittent nephrotic range proteinuria ± with epilepsy
DGKE[*]	AR	NM_003647	Hemolytic-uremic syndrome, SRNS
E2F3	AD	NM_001949	FSGS + mental retardation (whole gene deletion)
EMP2	AR	NM_001424	Childhood-onset SRNS and SSNS
INF2	AD	NM_022489	Familial and sporadic SRNS, FSGS-associated Charcot-Marie-Tooth neuropathy
ITGA3	AR	NM_002204	Congenital interstitial lung disease, nephrotic syndrome, and mild epidermolysis bullosa
ITGB4	AR	NM_000213	Epidermolysis bullosa and pyloric atresia + FSGS
KANK1	AR	NM_015158	SSNS
KANK2	AR	NM_015493	SSNS/SDNS ± hematuria
KANK4	AR	NM_181712	SRNS + hematuria
LAMB2[*]	AR	NM_002292	Pierson syndrome
LMNA	AD	NM_170707	Familial partial lipodystrophy + FSGS
LMX1B[*]	AD	NM_002316	Nail patella syndrome; also FSGS without extrarenal involvement
MYO1E[*]	AR	NM_004998	Familial SRNS
NUP93[*]	AR	NM_014669	Childhood SRNS
NUP107[*]	AR	NM_020401	Childhood SRNS
NUP205	AR	NM_015135	Childhood SRNS
NPHS1[*]	AR	NM_004646	CNS/SRNS
NPHS2[*]	AR	NM_014625	CNS, SRNS
NXF5	X-linked recessive	NM_032946	FSGS with co-segregating heart block disorder
OCRL[*]	X-linked recessive	NM_000276	Dent's disease-2, Lowe syndrome, ± FSGS, ± nephrotic range proteinuria
PAX2	AD	NM_003987	Adult-onset FSGS without extrarenal manifestations
PDSS2	AR	NM_020381	Leigh syndrome
PLCe1	AR	NM_016341	CNS/SRNS
PMM2	AR	NM_000303	Congenital disorder of glycosylation
PODXL[*]	AD	NM_005397	FSGS
PTPRO	AR	NM_030667	NS
SCARB2	AR	NM_005506	Action myoclonus renal failure syndrome ± hearing loss
SMARCAL1	AR	NM_014140	Schimke immuno-osseous dysplasia
SYNPO	AD	NM_007286	Sporadic FSGS (promoter mutations)
TRPC6[*]	AD	NM_004621	Familial and sporadic SRNS (mainly adult)
TTC21B	AR	NM_024753	FSGS with tubulointerstitial involvement
WDR73	AR	NM_032856	Galloway-Mowat syndrome (microcephaly and SRNS)
WT1[*]	AD	NM_024426	Sporadic SRNS (children: may be associated with abnormal genitalia); Denys-Drash and Frasier syndrome
XPO5	AR	NM_020750	Childhood SRNS
ZMPSTE24	AR	NM_005857	Mandibuloacral dysplasia with FSGS
MYH9	AD/assoc.	NM_002473	MYH9-related disease; Epstein and Fechtner syndromes
APOL1[*]	G1, G2 risk alleles	NM_003661	Increased susceptibility to FSGS and ESRD in African Americans, Hispanic Americans and in individuals of African descent

AD, autosomal dominant; AR, autosomal recessive; CNS, congenital nephrotic syndrome; DMS, diffuse mesangial sclerosis; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; NS, nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome; SSNS, steroid sensitive nephrotic syndrome.
*Genes with a likely or known mutation, or a risk allele, in this cohort.