Nephrotic Syndrome and Focal Segmental Glomerulosclerosis (NS/FSGS)

PANEL GENE LIST (55 GENES)

ACTN4, ADCK4 (COQ8B), ALG1, ANLN, APOL1*, ARHGAP24, ARHGDIA, CD2AP, COL4A3, COL4A4, COL4A5, COQ2, COQ6, CRB2, CUBN, DGKE, EMP2, FAN1, FAT1, FN1, GLA, INF2, ITGA3, ITGB4, KANK1, KANK2, KANK4, LAMB2, LMX1B, MAGI2, MYH9, MYO1E, NEIL1, NPHP1, NPHS1, NPHS2, NUP107, NUP205, NUP93, OCRL, PAX2, PDSS2, PLCE1, PMM2, PTPRO, SCARB2, SGPL1, SMARCAL1, STS, TBC1D8B, TRPC6, TTC21B, WDR73, WT1, XPO5

*G1 and G2 Risk Alleles Only

CLINICAL FEATURES AND GENETICS

Nephrotic syndrome (NS) is a clinically heterogeneous group of disorders characterized by proteinuria, hypertension, hypoalbuminemia, hypercholesterolemia and edema, which can ultimately lead to end-stage renal disease (ESRD). NS affects approximately 1-3 per 100,000 individuals worldwide and is considered one of the most common glomerular kidney diseases in children and adults.[1-2] Classification of NS may be based on an individual's response to steroids or according to pathologic findings on renal biopsy.[3] Aproximately 5-10% of individuals with NS, including approximately 10-15% of all affected children, do not respond to steroid therapy and are classified to have steroid-resistant nephrotic syndrome (SRNS), as opposed to steroid-sensitive nephrotic syndrome (SSNS).[4] Many studies have demonstrated that the incidence of disease in the population varies by age. Approximately 80% of individuals presenting with SRNS under the age of 1 have a genetics diagnosis, while this number drops to 26.5% for individuals presenting in childhood. Onset in adulthood is not as well studied and presentation is highly variable.[3]

On renal biopsy, the most common histopathologic changes observed in individuals with NS are either minimal change disease (MCD, most common in children with NS) or focal segmental glomerulosclerosis (FSGS, most common in adults with NS). FSGS is characterized by scarring in a limited number of kidney glomeruli and accounts for about 40% and 20% of adult and pediatric cases of NS, respectively.[2,5-6] While most cases of NS are reported to be sporadic due to secondary causes (such as diabetes, autoimmune disease, medication and infections), familial occurrence has been reported.[7-9] In the literature, the clinical term NS and the pathologic term FSGS are not always separated and might refer to the same disease entity. FSGS is a pattern of renal injury, and while some patients may also have nephrotic syndrome, others may only present with mild proteinuria.[10] In this panel, we have grouped together the NS and FSGS conditions to encompass a wider spectrum of renal disease. Overall, pathogenic variants in the ACTN4, ADCK4 (COQ8B), ARHGAP24, ARHGDIA, CD2AP, INF2, LAMB2, MYO1E, NPHS1, NPHS2, PLCE1, TRPC6 and WT1 genes are well-established in the literature in association with NS/FSGS. The majority of cases of SRNS are caused by variants in NPHS1, NPHS2 and WT1, while the majority of cases of FSGS are caused by variants in ACTN4 and INF2.[11-12]

The presence of specific variants in the APOL1 gene (c.1024A>G, p.Ser342Gly, a.k.a. G1 allele; c.1164_1169delTTATAA, p.Asn388_Tyr389del, a.k.a. G2 allele) is associated with increased risk of ESRD among individuals of recent African ancestry. Individuals with two risk alleles (homozygotes or compound heterozygotes) have a 10-17 fold higher odds of developing FSGS type 4 and a 29 fold higher risk of developing HIV-associated nephropathy, an increased risk of sickle cell-associated nephropathy, and shortened graft survival of kidney transplants based on the donor's genotype.[13-20] Of note, an individual positive for both G1 and G2 alleles is assumed to be a compound heterozygous because these alleles are in complete negative linkage disequilibrium.[15]

NS/FSGS may appear as a renal-only phenotype or may show features that overlap with other multi-system conditions, as in Alport syndrome (AS) and Coenzyme Q10 deficiency (CoQ10 deficiency). AS is characterized by progressive renal disease, mild to moderate sensorineural hearing loss, and ocular features.[21] Renal manifestations include hematuria, proteinuria, ultrastructural changes of the glomerular basement membrane and progression to ESRD.[22] Ocular symptoms are common and can include anterior lenticonus, central and peripheral fleck retinopathies, temporal retinal thinning and recurrent corneal erosions.[23] Recent literature has shown that variants in COL4A3, COL4A4 and COL4A5 genes, which are well-established AS genes, are additionally associated with FSGS and these patients are more likely to present with hematuria, family history and glomerular basement membrane abnormalities.[24] Coenzyme Q10 is involved in multiple cellular processes including mitochondrial respiratory activity. Defects in the nuclear encoded ADCK4 (COQ8B), COQ2, COQ6 and PDSS2 genes cause primary CoQ10 deficiency, an autosomal recessive mitochondrial disorder that presents with SRNS, encephalopathy and slowly-progressive multiple system atrophy-like phenotype. Age of onset ranges from birth to the seventh decade and may vary in severity.[25] Primary CoQ10 deficiency accounts for up to 2% of NS.[26]

Other genes previously reported to be associated with NS/FSGS and/or with pathogenic variants causing similar presentation included in this panel are ALG1, ANLN, CRB2, CUBN, DGKE, EMP2, FAN1, FAT1, FN1, GLA, ITGA3, ITGB4, KANK1, KANK2, KANK4, LMX1B, MAGI2, MYH9, NEIL1, NPHP1, NUP107, NUP205, NUP93, OCRL, PAX2, PMM2, PTPRO, SCARB2, SGPL1, SMARCAL1, STS, TBC1D8B, TTC21B, WDR73 and XPO5.

TEST METHODS

Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. For the APOL1 gene, only the G1 and G2 risk alleles are evaluated. For the SGPL1 and TBC1D8B genes, sequencing but no copy number testing is performed. For the ALG1 and ARHGDIA genes, only whole gene deletions or duplications may be reported. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

TECHNICAL TEST SENSITIVITY

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events, but less for deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

CLINICAL TEST SENSITIVITY

NS/FSGS is a genetically heterogeneous disorder. The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype and family history. Additional information about the general clinical sensitivity of each gene is included in the table below.

Gene	Protein	Inheritance	Disease Association	Sensitivity
ACTN4	Actinin, Alpha-4	AD	FSGS 1	~3% of FSGS[12]
ADCK4 (COQ8B)	Coenzyme Q8B	AR	NS 9	34/79 individuals with CoQ10 Deficiency[25] ~2-7% of SRNS[27-29]
ALG1	Asparagine-Linked Glycosylation 1 Homolog	AR	CDG Type 1k	~90-100% of CDG Type 1k[30-32]
ANLN	Actin-Binding Protein Anillin	AD	FSGS 8	~1% of FSGS[33]
APOL1	Apolipoprotein L-I	AR	G1 and G2 Risk Alleles for ESRD / FSGS 4	In large population databases, the G1 and G2 alleles account for about 14% and 23% of APOL1 alleles among individuals with African ancestry, respectively[17,34]
ARHGAP24	Rho GTPase-Activating Protein 24	AD	FSGS	Rare[35]
ARHGDIA	Rho GDP-Dissociation Inhibitor Alpha	AR	NS 8	Rare[36-38]
CD2AP	CD2 Associated Protein	AD/AR	FSGS 3	Rare[5,39-41]
COL4A3	Collagen, type IV, alpha-3	AD/AR	AS	~12-15% of AS[42-44] 5/93 individuals with NS[24,45]
COL4A4	Collagen, type IV, alpha-4	AD/AR	AS	~5-8% of AS[42-44] 10/93 individuals with NS[24,45]
COL4A5	Collagen, type IV, alpha-5	XL	AS / AS-DL / AMME	~80-85% of AS[42-44] 8/93 individuals with NS[24,45]
COQ2	Coenzyme Q2, Polyprenyltransferase	AR	Primary CoQ10 Deficiency 1	10/79 individuals with CoQ10 Deficiency[25]
COQ6	Coenzyme Q10 Monooxygenase 6	AR	Primary CoQ10 Deficiency 6	5/79 individuals with CoQ10 Deficiency[25]
CRB2	Crumbs Cell Polarity Complex Component 2	AR	FSGS 9 / Ventriculomegaly with Cystic Kidney Disease	Rare[46-49]

CUBN	Cubilin	AR	Megaloblastic Anemia-1, Finnish type	Rare[11,29]
DGKE	Diacylglycerol Kinase Epsilon	AR	NS 7	Rare[11,50]
EMP2	Epithelial Membrane Protein 2	AR	NS 10	Rare[51]
FAN1	FANCD2 and FANCI Associated Nuclease 1	AR	Interstitial Nephritis	Rare[52]
FAT1	FAT Atypical Cadherin 1	AR	CAKUT / NS	Rare[53]
FN1	Fibronectin 1	AD	Glomerulopathy with Fibronectin Deposits	Rare[54-55]
GLA	Galactosidase, Alpha	XL	Fabry disease	~90-100% of Fabry Disease[56]
INF2	Inverted Formin 2	AD	FSGS 5	~10% of FSGS[12]
ITGA3	Integrin, Alpha-3	AR	ILNEB	Rare[11,57-58]
ITGB4	Integrin, Beta-4	AR	Epidermolysis Bullosa	Rare[11,59-60]
KANK1	KN Motif and Ankyrin Repeat Domains 1	AR	NS	Rare[61]
KANK2	KN Motif and Ankyrin Repeat Domains 2	AR	NS 16	Rare[61]
KANK4	KN Motif and Ankyrin Repeat Domains 4	AR	NS	Rare[61]
LAMB2	Laminin, Beta-2	AR	NS 5 / Pierson syndrome	Rare[11,62-64]
LMX1B	LIM Homeobox Transcription Factor 1, Beta	AD	Nail-Patella syndrome	~95% of Nail-Patella syndrome[65]
MAGI2	Membrane-Associated Guanylate Kinase, WW And PDZ Domains-Containing, 2	AR	NS 15	Rare[66]
MYH9	Myosin, Heavy Chain 9, Nonmuscle	AD	AS-like syndrome with Macrothrombocytopenia	~98% of MYH9-Related Disorders[67]
MYO1E	Myosin 1E	AR	FSGS 6	Rare[68-69]
NEIL1	Endonuclease VIII-Like 1	AR	NS	Rare[69]
NPHP1	Nephrocystin 1	AR	JS 4 / NPHP 1 / SLS 1	~15-20% of NPHP-RC[70-71]
NPHS1	Nephrin	AR	NS 1	~5-14% of SRNS[4,28,72]
NPHS2	Podocin	AR	NS 2	~10-40% of SRNS[11,28,72]

NUP107	Nucleoporin, 107-KD	AR	GAMOS 7 / NS 11	Rare[73,74]
NUP205	Nucleoporin, 205-KD	AR	NS 13	Rare[75]
NUP93	Nucleoporin, 93-KD	AR	NS 12	Rare[75]
OCRL	Inositol Polyphosphate 5-Phosphatase OCRL-1	XL	Lowe syndrome / Dent disease	~15% of Dent Disease[76] ~90-100% of Lowe syndrome[77]
PAX2	Paired Box 2	AD	FSGS 7 / Papillorenal syndrome	~4% of FSGS[78]
PDSS2	Prenyl Diphosphate Synthase, Subunit 2	AR	Primary CoQ10 Deficiency 3	2/79 individuals with CoQ10 Deficiency[25]
PLCE1	Phospholipase C, Epsilon-1	AR	NS 3	29/45 individuals with NS/FSGS[11]
PMM2	Phosphomannomutase 2	AR	CDG Type 1a	~90-100% of CDG Type 1a[30,79-80]
PTPRO	Protein-Tyrosine Phosphatase, Receptor-Type, O	AR	NS 6	Rare[81]
SCARB2	Scavenger Receptor Class B, Member 2	AR	AMRF	~97% of AMRF[82]
SGPL1	Sphingosine-1-Phosphate Lyase 1	AR	NS 14	35 families with FSGS[83]
SMARCAL1	SWI/SNF-Related, Matrix-Associated, Actin-Dependent Regulator of Chromatin, Subfamily A-Like Protein 1	AR	SIOD	13/18 individuals with FSGS[11] ~90% of SIOD[84]
STS	Steroid Sulfatase	XL	Ichthyosis (with or without NS)	3 individuals with NS and STS deletion[85-87]
TBC1D8B	TBC1 Domain Family, Member 8B	XL	NS 20	Rare[88]
TRPC6	Transient Receptor Potential Cation Channel, Subfamily C, Member 6	AD	FSGS 2	~2% of FSGS[12]
TTC21B	Tetratricopeptide Repeat Domain-Containing Protein 21b	AR	NPHP 12 / FSGS	10/61 individuals with FSGS[89-90]
WDR73	WD Repeat-Containing Protein 73	AR	GAMOS 1	~1% of SRNS[91-92]
WT1	WT1 Transcription Factor	AD	NS 4 / DD / FS	~2-4% of SRNS[2,11,28]

XPO5	Exportin 5	AR	NS	Rare[75]

AD – Autosomal Dominant; AR – Autosomal Recessive; XL – X-Linked
AMRF – Action Myoclonus-Renal Failure syndrome; AS – Alport syndrome; AS-DL – Alport syndrome with Diffuse Leiomyomatosis; AMME – Alport syndrome, Mental retardation, Midface hypoplasia and Elliptocytosis; CDG – Congenital Disorders of Glycosylation; DD – Denys-Drash syndrome; FS – Frasier syndrome; FSGS – Focal Segmental Glomerulosclerosis; GAMOS – Galloway-Mowat syndrome; ILNEB – Interstitial Lung Disease, Nephrotic syndrome, and Epidermolysis Bullosa; JS – Joubert syndrome; NPHP – Nephronophthisis; NPHP-RC – Nephronophthisis Related Ciliopathy; NS – Nephrotic syndrome; SIOD – Schimke Immunoosseous Dysplasia; SLS – Senior Loken syndrome; SRNS – Steroid Resistant Nephrotic syndrome

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