

La genetica nella sindrome nefrosica: quando?

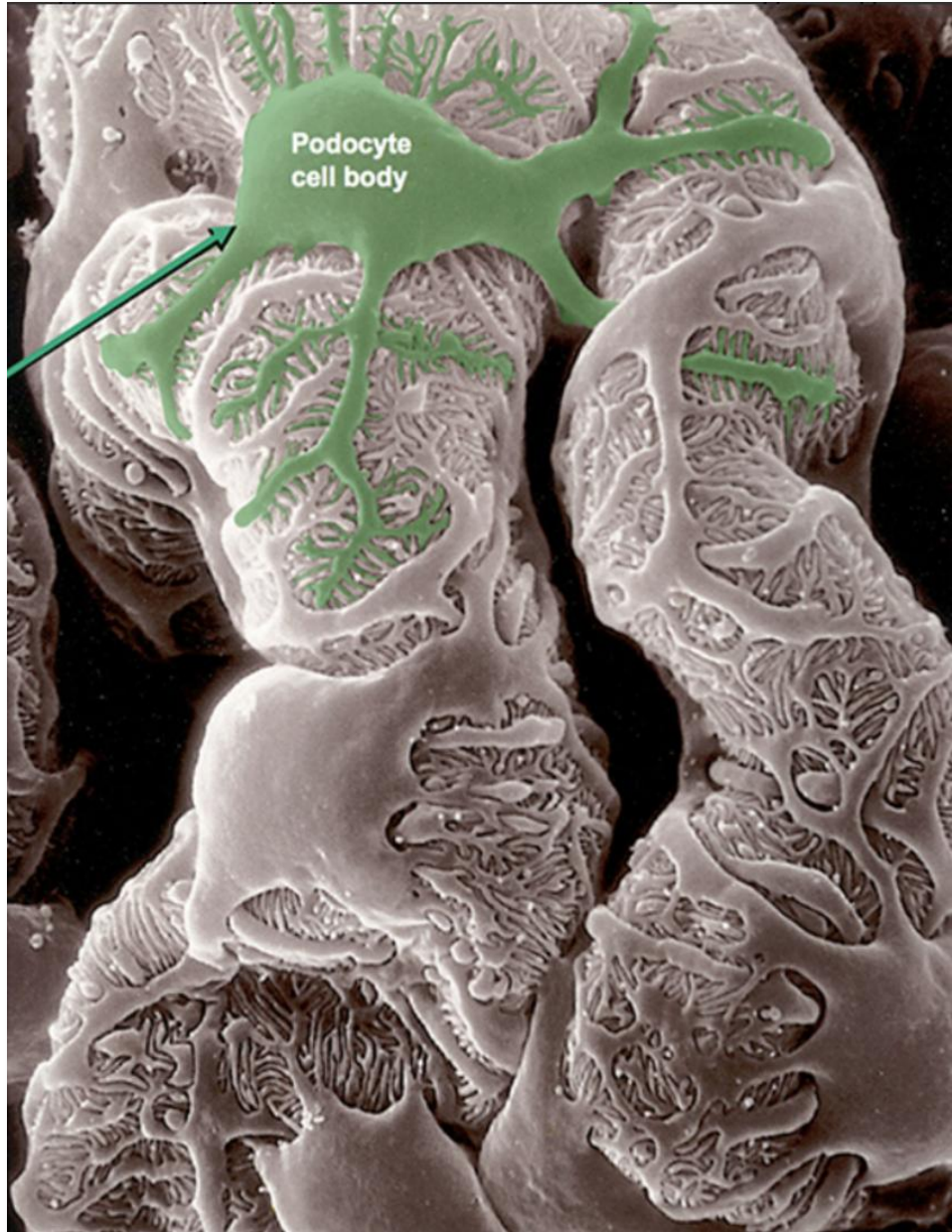
Paola Romagnani



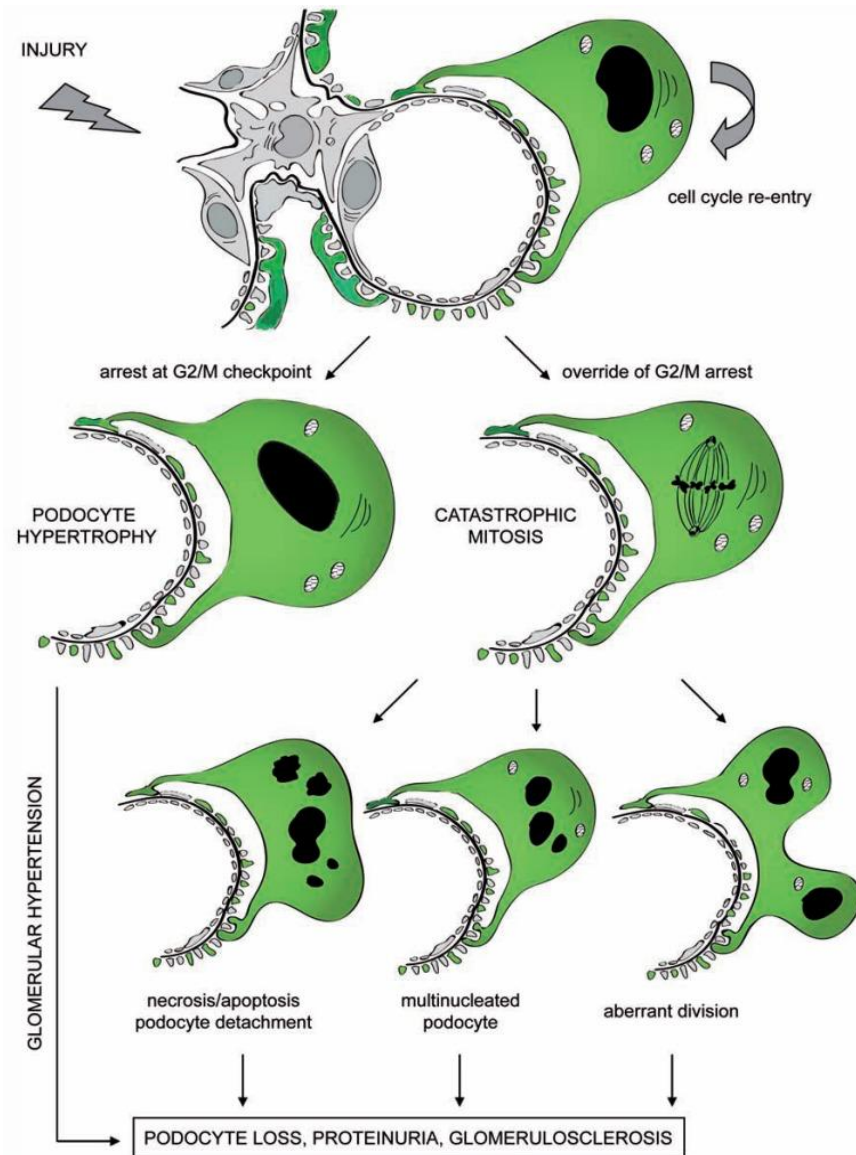
Roma, 27 Aprile, 2019



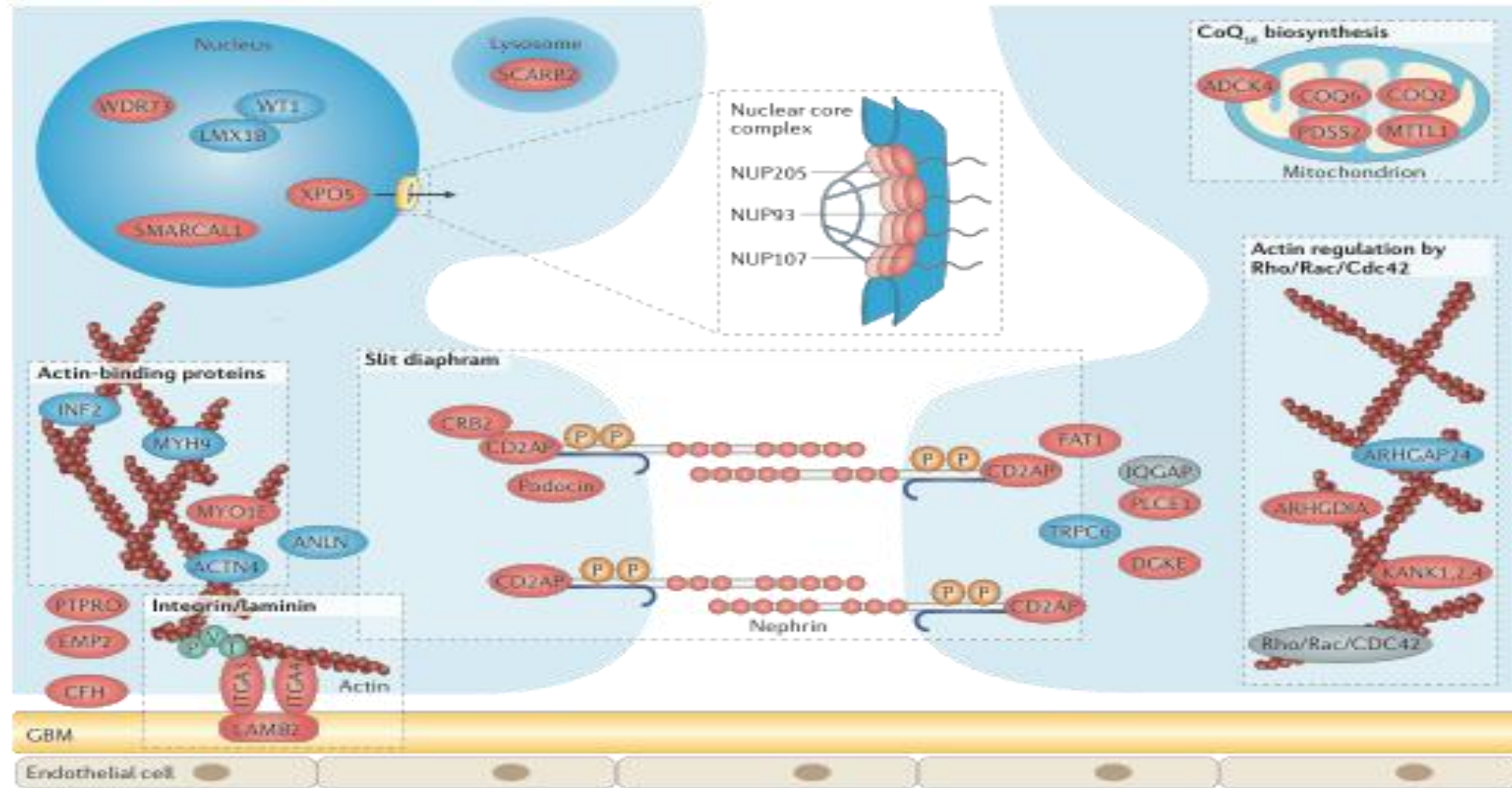
Glomerulus repair



Podocyte mitosis: a catastrophe!

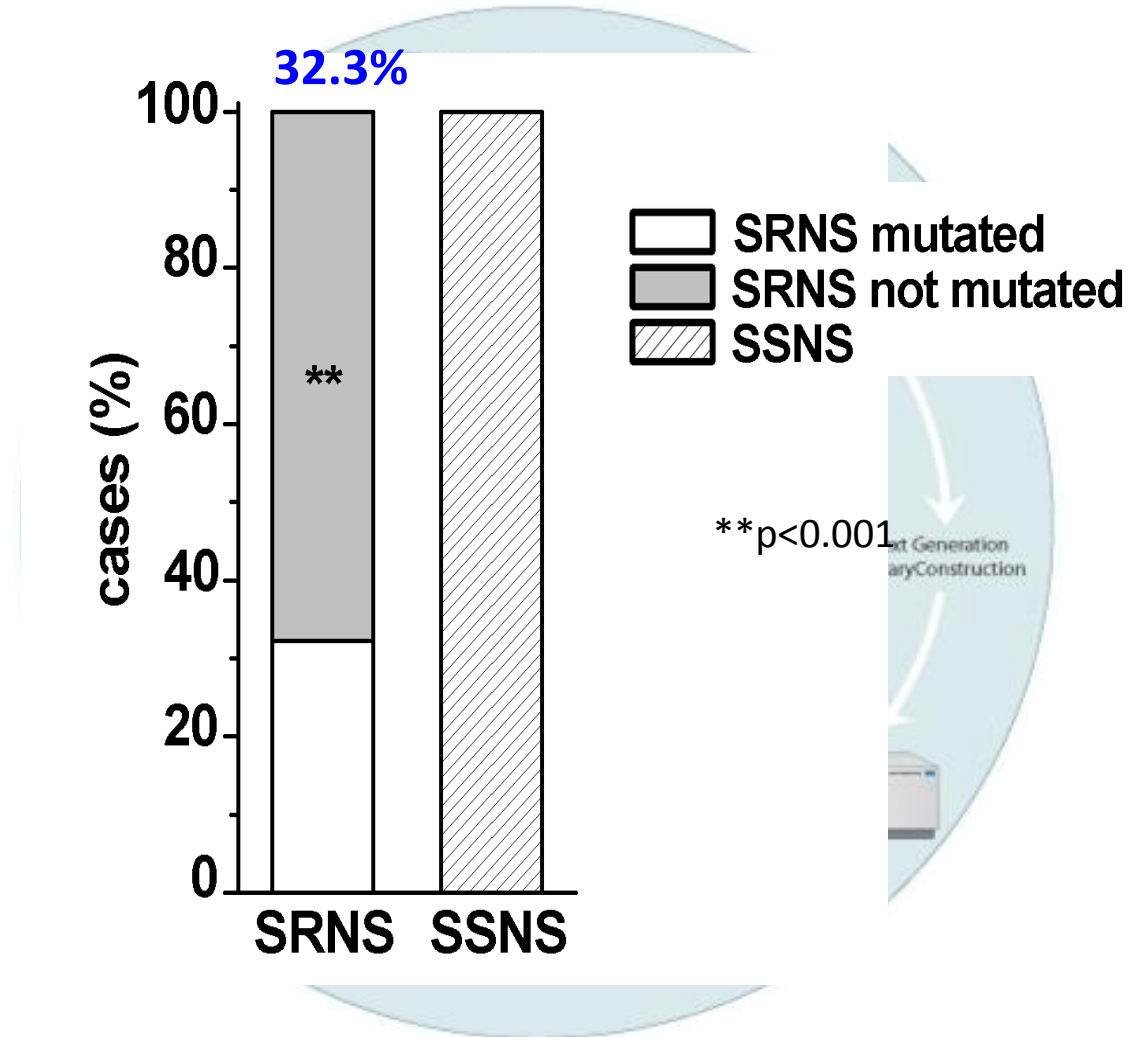


Pathogenic pathways of steroid resistant nephrotic syndrome



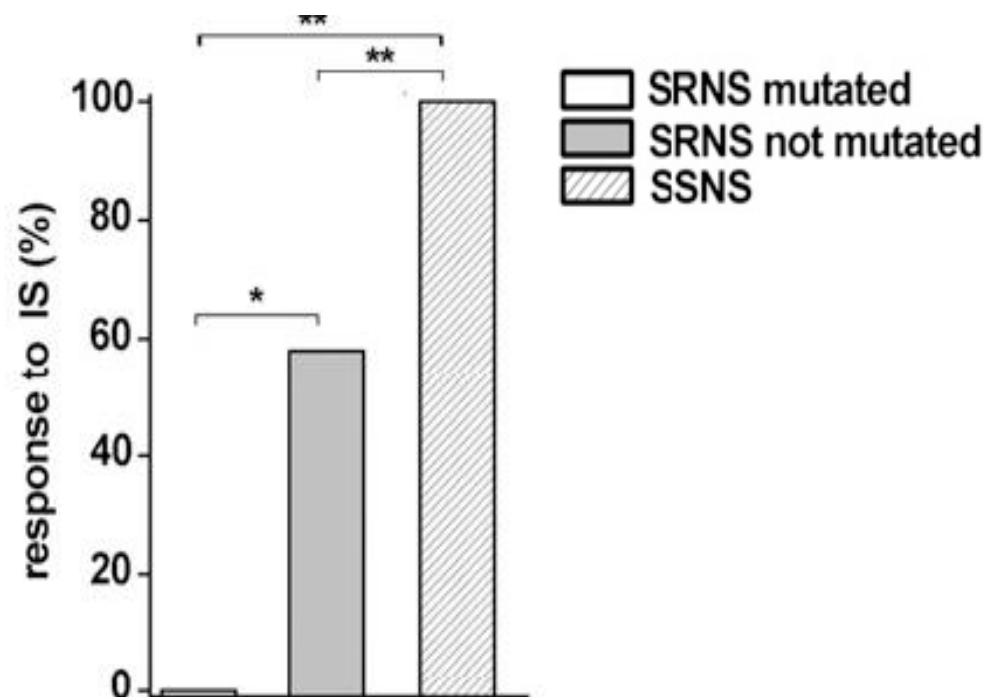
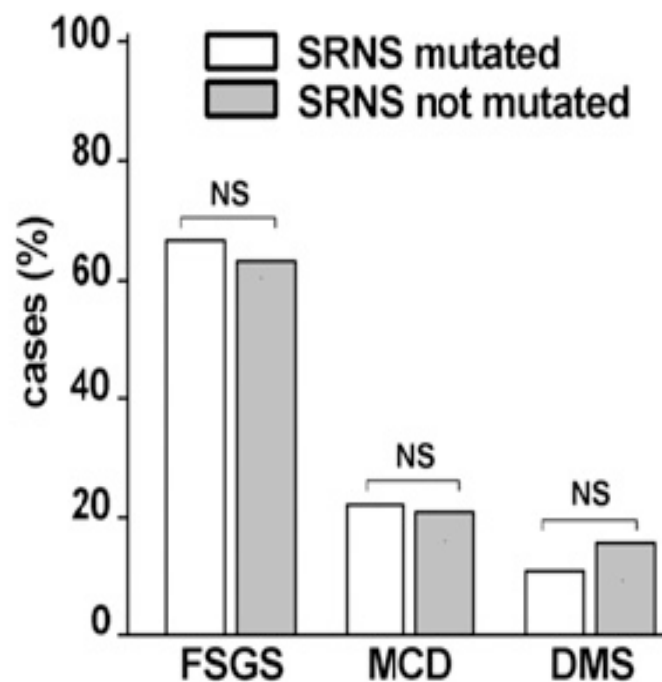
Gene	Protein	Locus	Exons	RefSeq
WT1	Wilms tumor	chr11:32409325-32457087	10	NM_024426
LMX1B	LIM homeobox transcription factor 1, beta	chr9:129376748-129463311	8	NM_002316
NPHS1	nephrin	chr19:36316274-36342739	29	NM_004646
NPHS2	podocin	chr1:179519677-179545084	8	NM_014625
CD2AP	CD2-associated protein	chr6:47445525-47594994	18	NM_012120
ACTN4	actinin, alpha 4	chr19:39138327-39221170	21	NM_004924
INF2	inverted formin 2	chr14:105155943-105185947	23	NM_022489
ITGA3	integrin alpha 3	chr17:48133340-48167848	26	NM_002204
TRPC6	transient receptor potential cation channel,6	chr11:101322296-101454659	13	NM_004621
LAMB2	laminin, beta 2	chr3:49158548-49170599	33	NM_002292
PLCE1	phospholipase C, epsilon 1	chr10:95753746-96088146	32	NM_016341
SCARB2	scavenger receptor class B, member 2	chr4:77079894-77135035	12	NM_005506
CoQ2	para-hydroxybenzoate-polyprenyltransferase,	chr4:84184979-84205964	7	NM_015697
PDSS2	prenyl diphosphate synthase, subunit 2	chr6:107473761-107780779	8	NM_020381
SMARCA1	SWI/SNF-related matrix-associated	chr2:217277473-217347772	18	NM_001127207
ZMPSTE24	zinc metallo-peptidase STE24	chr1:40723733-40759855	10	NM_005857
MYH9	myosin, heavy polypeptide 9, non-muscle	chr22:36677324-36784063	42	NM_002473
PTPRO	receptor-type protein tyrosine phosphatase O	chr12:15475487-15750335	27	NM_030667
MYO1E	myosin IE	chr15:59428564-59665071	28	NM_004998
PAX2	paired box 2	chr10:102505468-02589697	11	NM_003990
ARHGDIA	rho GDP dissociation inhibitor (GDI) alpha	chr17:79825597-9829282	6	NM_004309
ARHGAP24	rho GTPase activating protein 24	chr4:86396284-86923823	10	NM_001025616
CUBN	Cubilin	chr10:16865965-17171816	67	NM_001081
ANLN	anillin actin binding protein	chr7:36429432-36493400	24	NM_018685
TTC21B	tetratricopeptide repeat domain 21B	chr2:166729872-166810348	29	NM_024753
COL4A3	collagen type IV alpha 3	chr2:228029281-228179508	52	NM_000091
COL4A4	collagen type IV alpha 4	chr2:227867427-228029275	48	NM_000092
COL4A5	collagen type IV alpha 5	chrX:107683074-107940775	53	NM_033380
COL4A6	collagen type IV alpha 6	chrX:107398837-107681658	45	NM_033641

About 30% of children that are steroid resistant carry potentially pathogenic genetic alteration



Heterogeneous Genetic Alterations in Sporadic Nephrotic Syndrome Associate with Resistance to Immunosuppression

Sabrina Giglio,^{*†} Aldesia Provenzano,^{*} Benedetta Mazzinghi,[†] Francesca Becherucci,[‡] Laura Giunti,[†] Giulia Sansavini,[‡] Fiammetta Ravaglia,[‡] Rosa Maria Roperto,[‡] Silvia Farsetti,[‡] Elisa Benetti,[§] Mario Rotondi,^{||} Luisa Murer,[§] Elena Lazzeri,[¶] Laura Lasagni,[¶] Marco Materassi,[‡] and Paola Romagnani^{*¶}

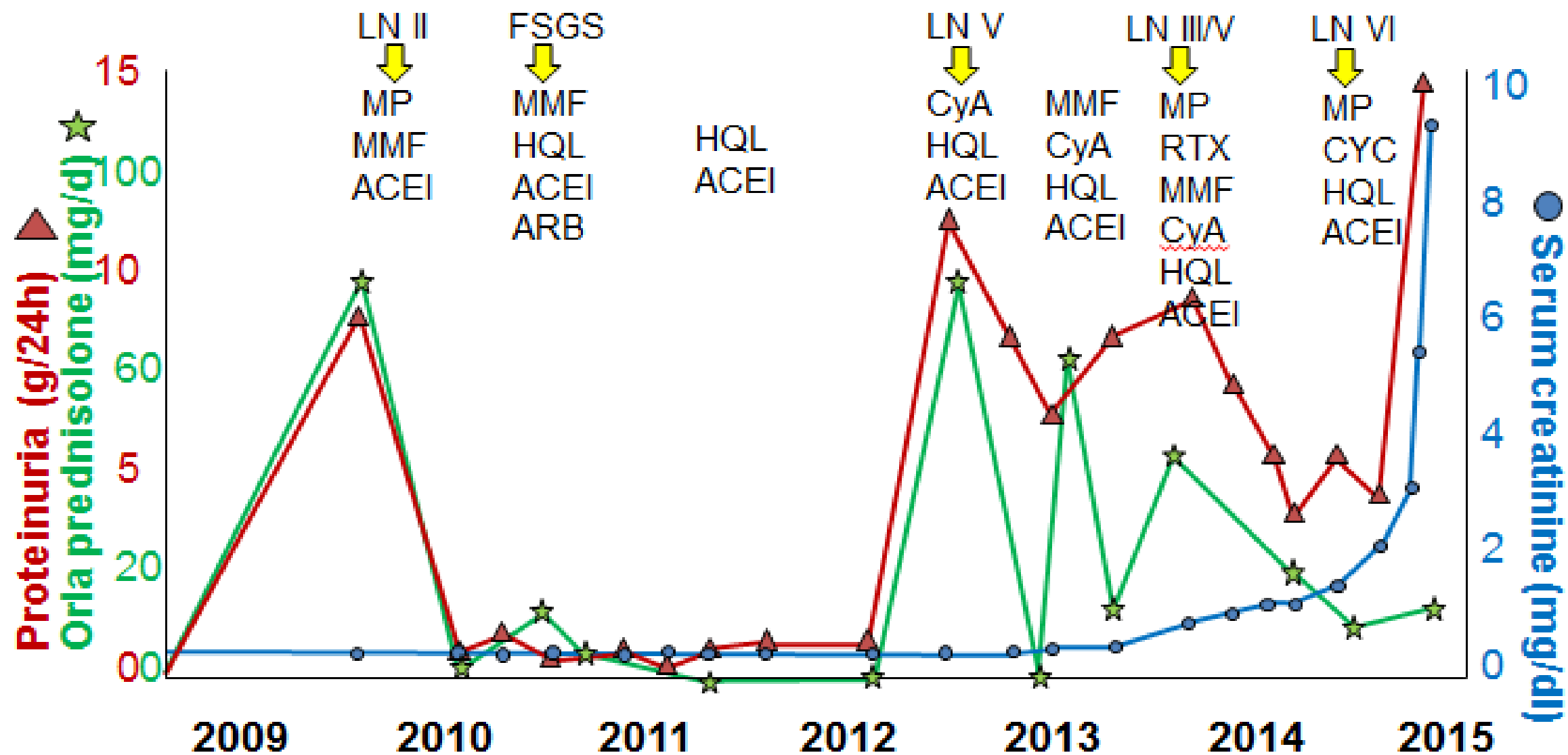


The Bench-to-Bedside Transition

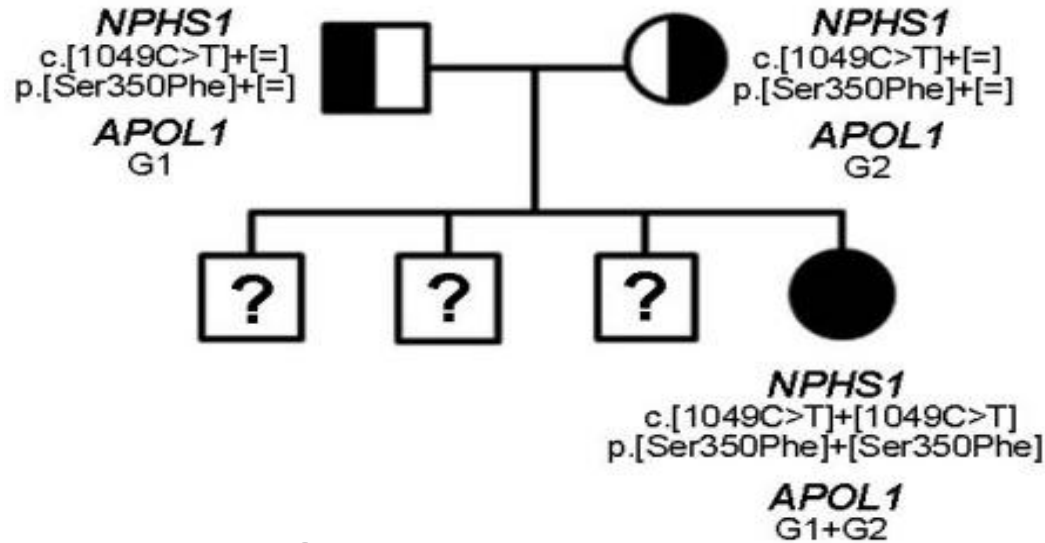
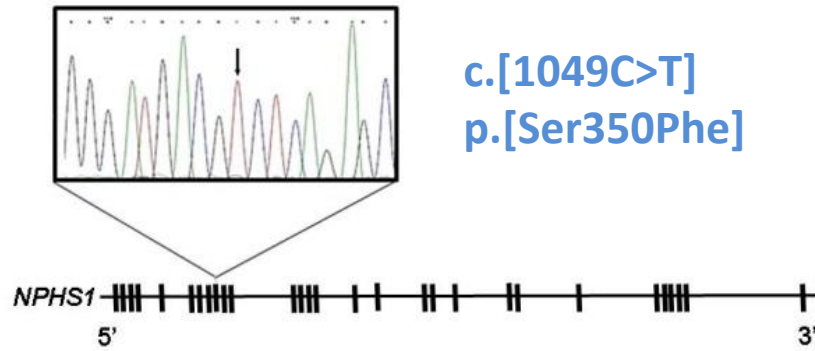
Next generation sequencing and functional analysis of patient urine renal progenitor-derived podocytes to unravel the diagnosis underlying refractory lupus nephritis

Paola Romagnani^{1,2,*}, Sabrina Giglio^{1,3,*}, Maria Lucia Angelotti⁴, Aldesia Provenzano³, Francesca Becherucci², Benedetta Mazzinghi², Susanna Müller⁵, Kerstin Amann⁶, Marc Weidenbusch⁷, Simone Romoli⁷, Elena Lazzeri⁴ and Hans-Joachim Anders⁷

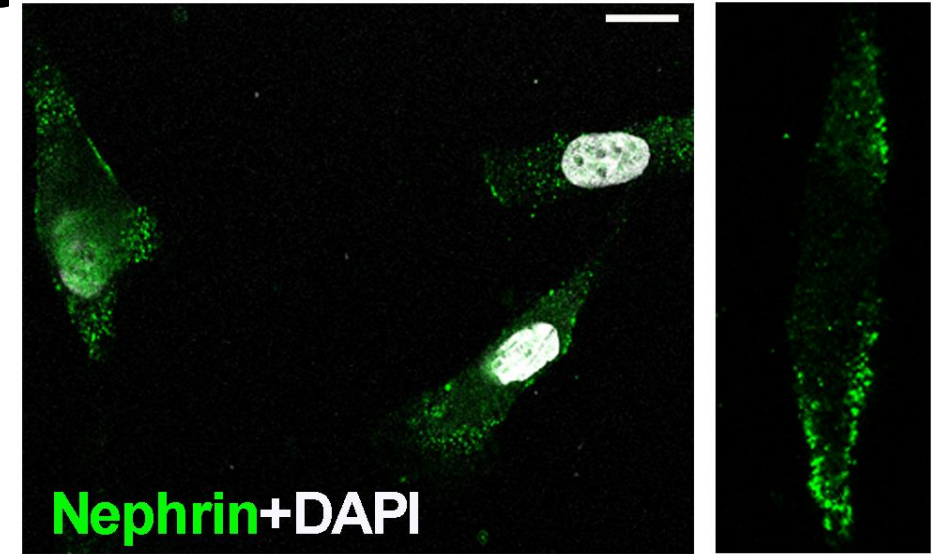
¹Department of Biomedical Experimental and Clinical Sciences ‘Mario Serio’, Florence, Italy, ²Nephrology and Dialysis Unit, Meyer Children’s University Hospital, Florence, Italy, ³Medical Genetic Unit, Meyer Children’s University Hospital, Florence, Italy, ⁴Excellence Centre for Research, Transfer and High Education for the Development of De Novo Therapies (DENOTHE), University of Florence, Florence, Italy, ⁵Pathologisches Institut, Ludwig-Maximilians Universität, München, Germany, ⁶Department of Nephropathology, University of Erlangen-Nürnberg, Erlangen, Germany and ⁷Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Klinikum der LMU München, Innenstadt, Munich, Germany



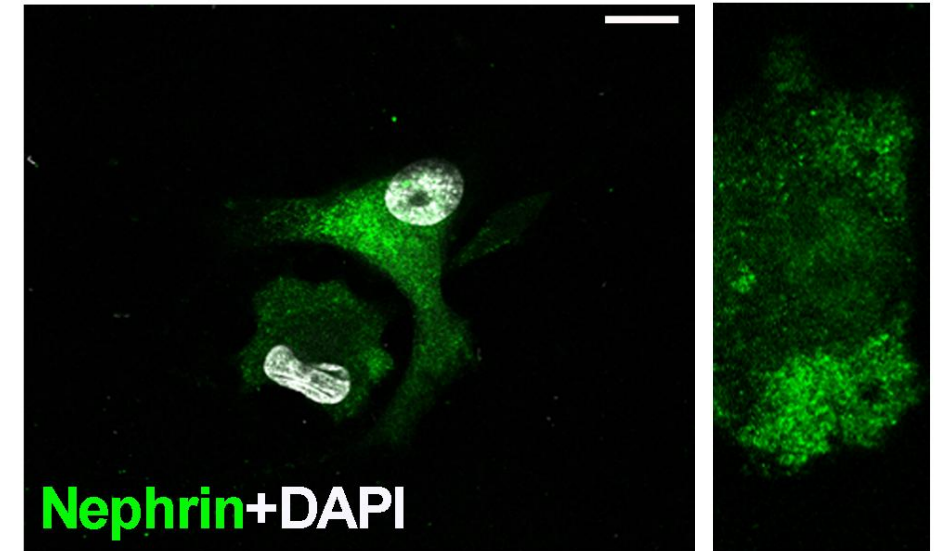
Identification and functional validation of an homoizigous variant in NPHS1 gene by next generation sequencing



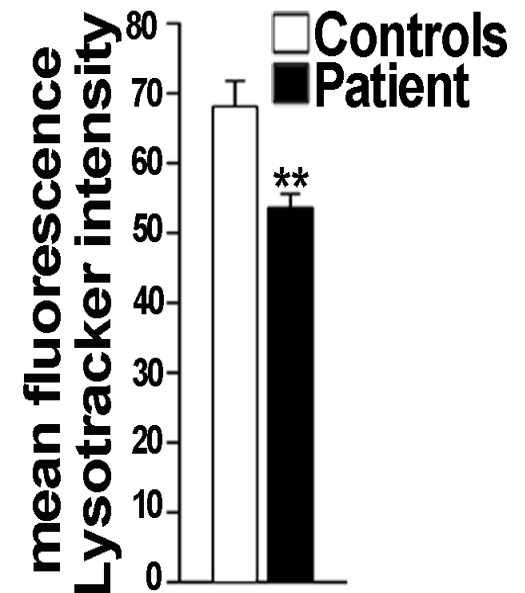
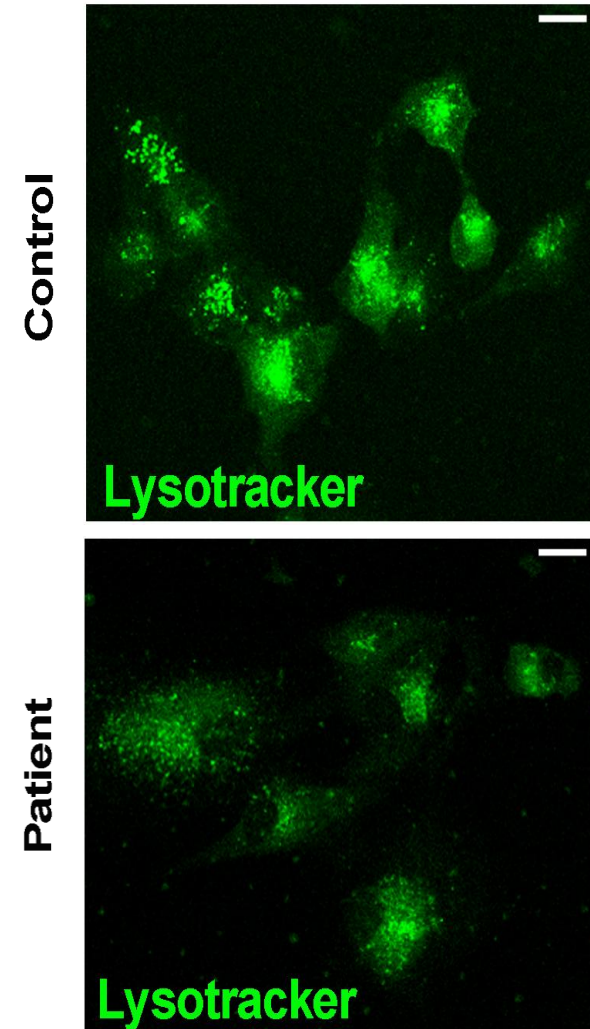
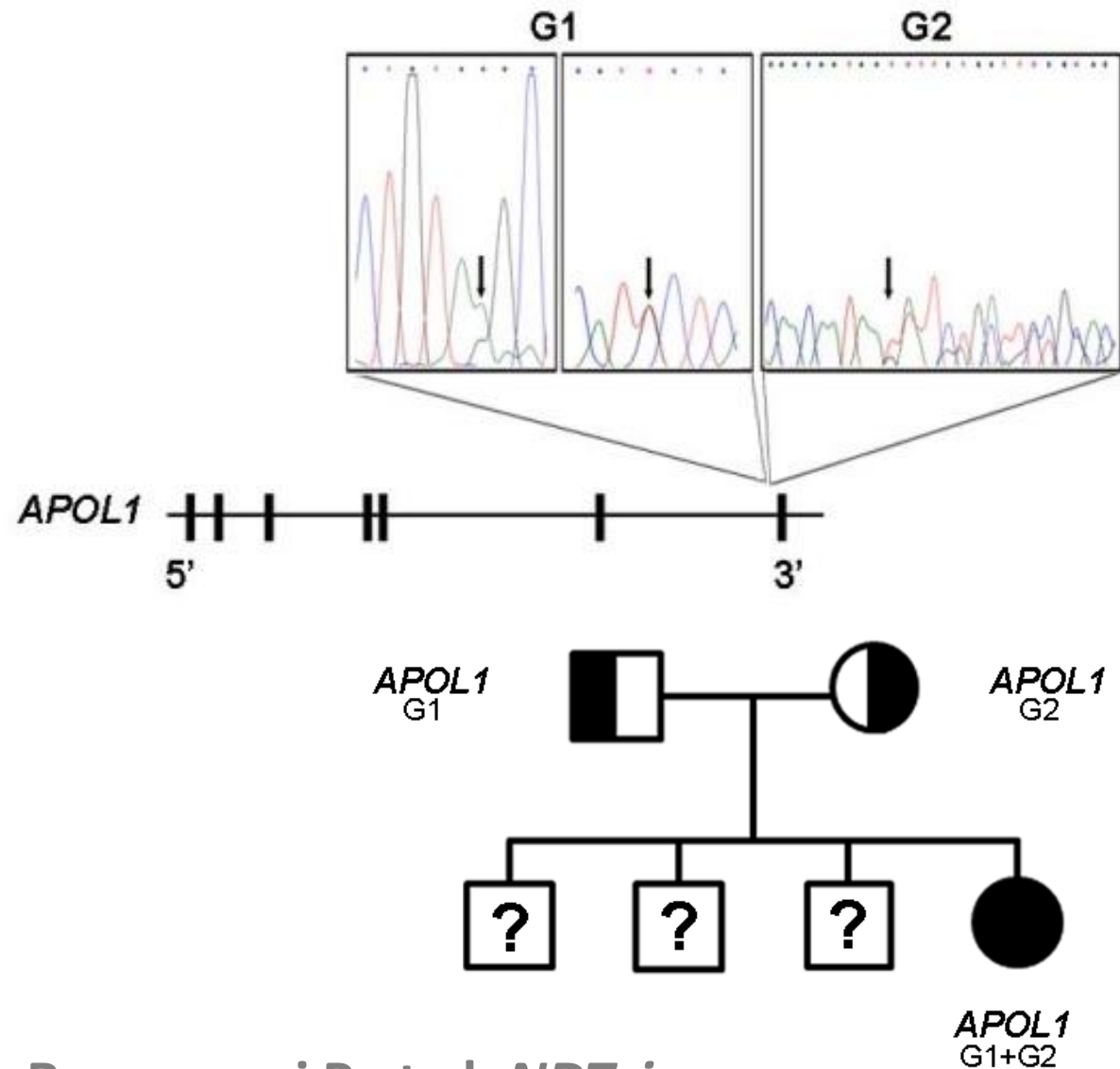
Control



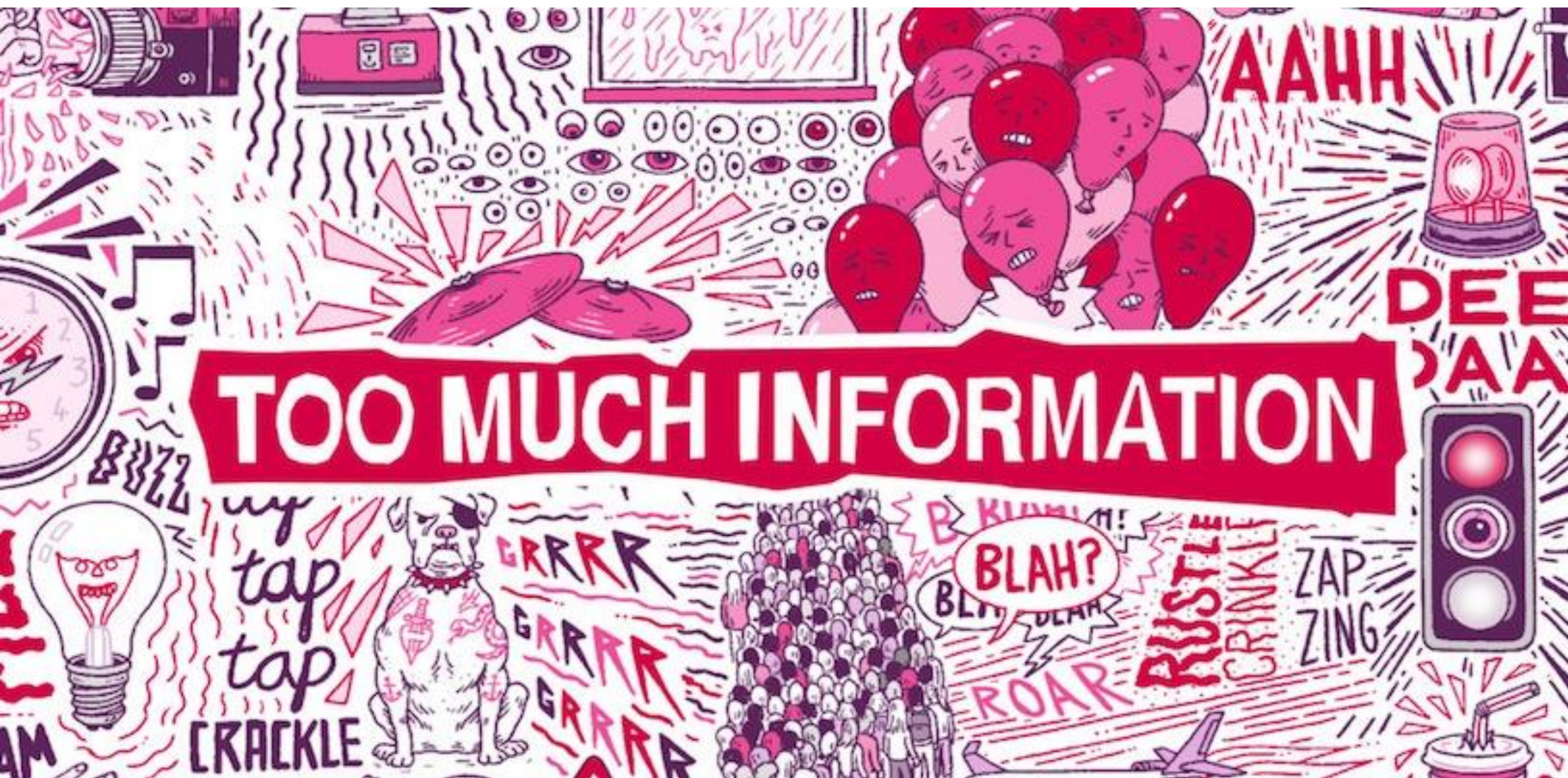
Patient



Genetic and functional evaluation of APOL1 risk alleles





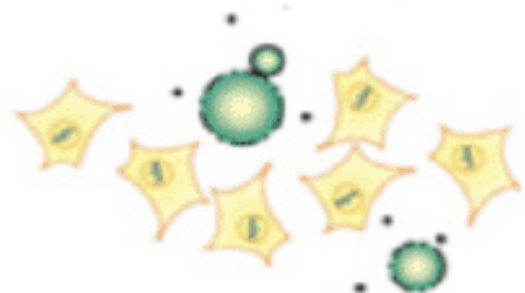


Forward Genetics

Discover
Gene
underlying
Phenotype

Mutagenesis,
QTL mapping,
Positional
cloning, etc...

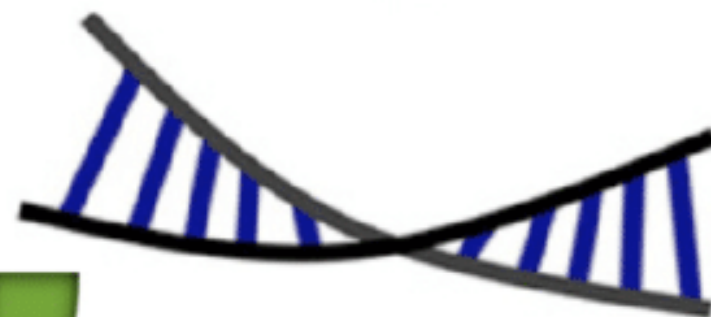
Known Phenotype



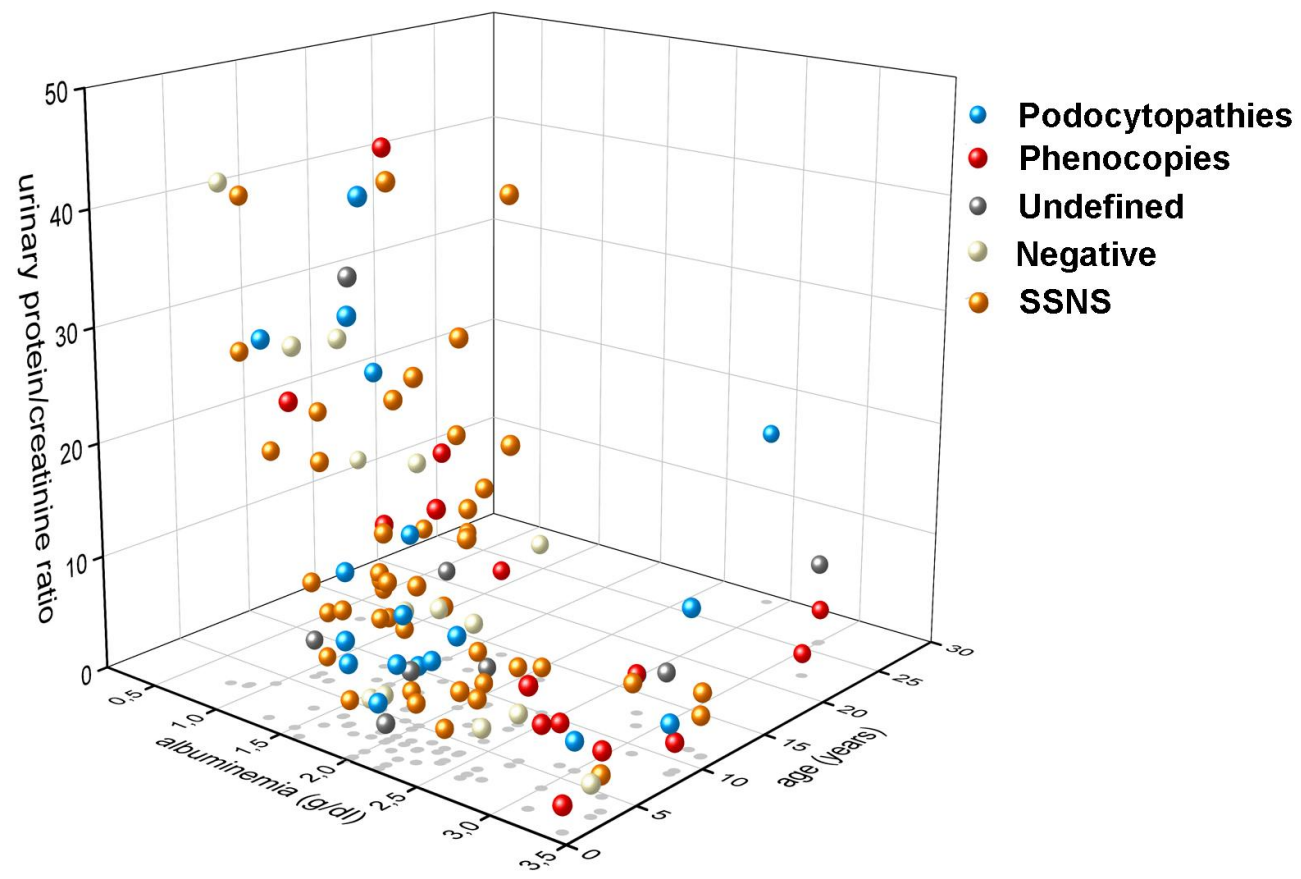
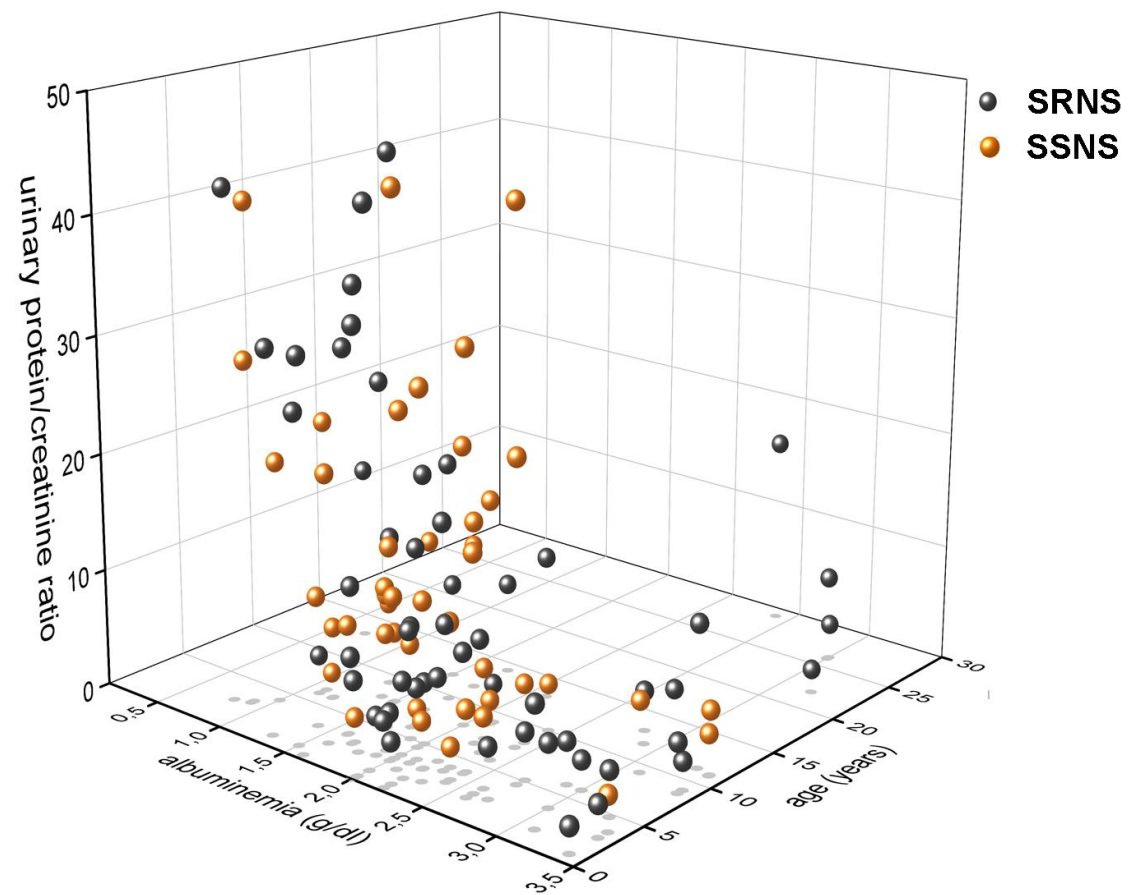
Phenotype
Resulting
from
Alteration

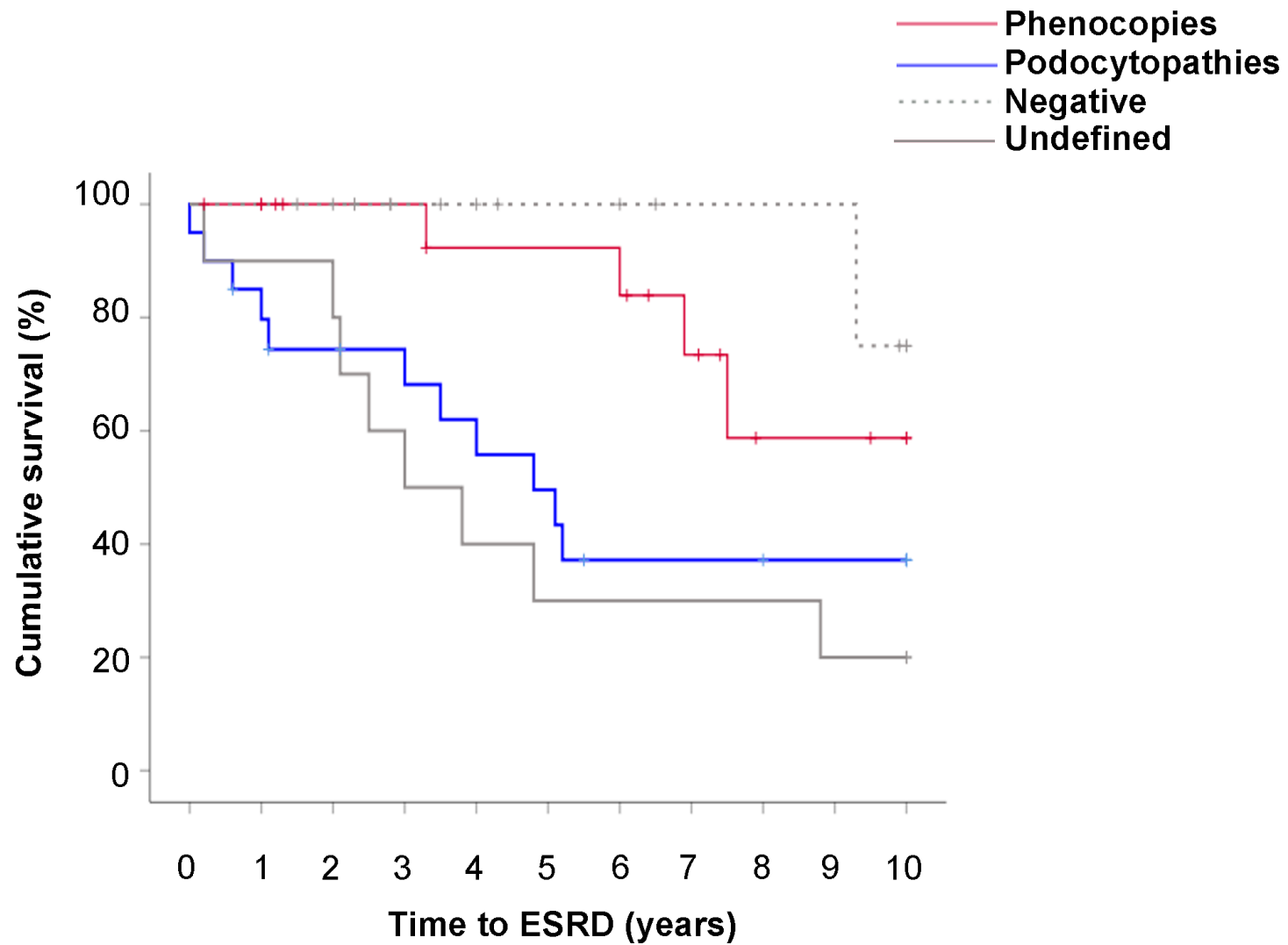
Ectopic expression,
Gene silencing,
Gene targeting,
TILLING, etc...

Known Gene



Reverse Genetics





Phenocopies	18	17	13	13	11	11	11	7	3	3	2
Podocytopathies	20	16	13	12	10	8	5	5	5	4	4
Negative	15	15	14	9	8	6	6	4	4	4	3
Undefined	10	9	9	6	4	3	3	3	3	2	2
Total	63	57	49	40	33	28	25	19	15	13	11

ARTICLE

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OPEN

Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment

Shazia Ashraf et al.[#]

