Supplemental Methods

Participants and CNV Original Study

The CKiD study is a multicenter prospective, observational study of children with mild-to-moderate CKD. Eligibility criteria for enrollment in CKiD includes age 1-16 years, an estimated GFR of 30-90ml/min per 1.73m^2 and exclusion criteria include previous malignancy, transplantation, or dialysis within the previous 3 months, genetic syndromes involving the central nervous system, history of severe to profound intellectual disability, and a limited number of other conditions. Subjects were seen initially at a baseline study visit and then at another study visit 3-6 months later, at which point neurocognitive and psychosocial data were collected.[1] CKiD DNA samples were genotyped on Illumina HumanOmni2.5 arrays.

In the original CNV study[2] variants were called and quality controlled using Illumina GenomeStudio, Plink[3] and PennCNV[4] in CKiD participants and 21,575 population controls genotyped in Illumina Hap550 and higher arrays. Controls included a cohort of 1,890 healthy children from the Children's Hospital of Philadelphia.

Measures of Neurocognitive and Psychosocial Function and Clinical and Demographic Variables from the CKiD study

The MSEL (subjects 12 months-29 months), WPPSI-R (subjects 30 months to 71 months), and WASI (subjects 6 years of age and older) are standardized measures of intelligence. The WIAT-II-A is a standardized measure of academic achievement for children 6 years and older. All four tests are reported as standardized scores with mean 100 and standard deviation of 15; higher scores indicate better performance. The BRIEF is a parent completed inventory that measures executive function for children 6 years and older and has a mean of 50 and standard deviation of 10; lower scores indicate better performance. The BASC-II measures behavioral and emotional symptoms for children 2-18 years. The externalizing problems score examines areas of hyperactivity, aggression and conduct problems. The internalizing problems score evaluates areas of depression, anxiety and somatization. The adaptive skills score examines pro-social, desirable

behaviors and the behavioral symptoms index score measures the overall level of behavioral problems. All subset scale scores on the BASC-II have a mean of 50 with a standard deviation of 10. A higher score indicates better adaptive symptoms and a lower score indicates fewer symptoms for the behavior symptoms, externalizing problems, and internalizing problems composite scores.

Bedside eGFR was calculated as 41.3 x height/SCr, where height is in meters.[5] It was modeled as log transformed in multivariate regression models.

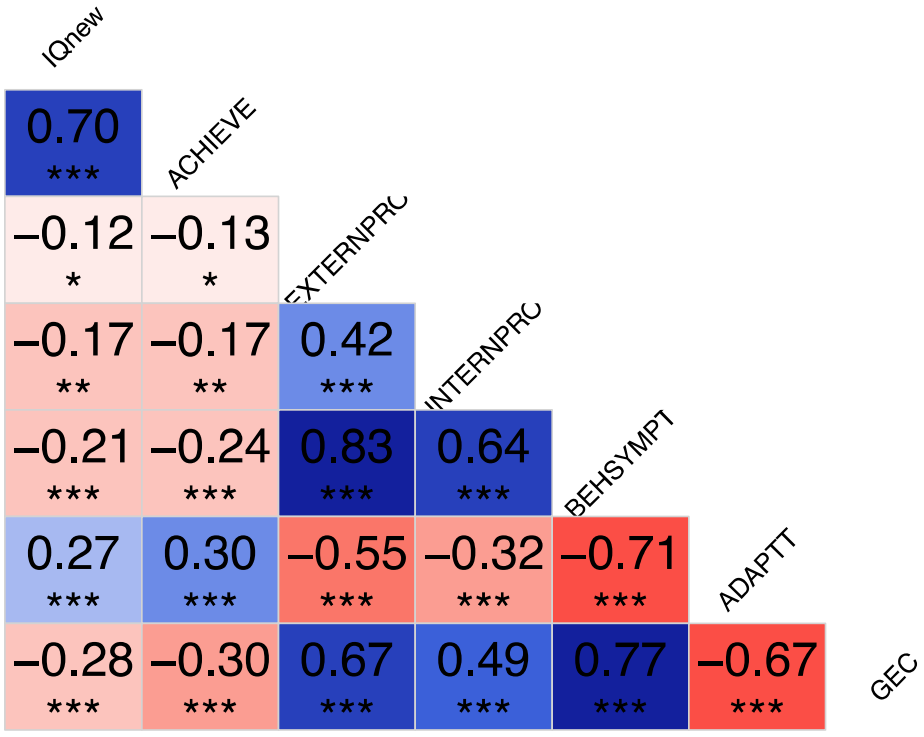
Disease Duration is defined as: Age at neurocognitive evaluation minus age at CKD onset, in years.

For multivariate analyses covariates with > 5% missing values in the sample set or among carriers were excluded.

Statistical Software

Principal component analysis was performed with Eigensoft software package[6] on CKiD participants' SNP genotyping data pre-processed using Illumina GenomeStudio and Plink. All other statistical analyses and plots were done using Microsoft R Open 3.2.3 in RStudio 0.99.

Supplementary Figure 1. Intercorrelation between NC outcome variables. Pairwise Pearson correlation coefficients are shown, for the NC outcomes indicated in the diagonal . Asterisks indicate significance of the correlation (***, ** and * for p < 5x10-4, p < 5x10-3 and p<5x10-2, respectively). Color hue and shade represent sign and magnitude of the coefficients, respectively.



Supplementary Table 1. NC outcome variables values in GD carriers. Each row represents an individual carrying a known pathogenic GD (19 individuals, upper panel) or a likely pathogenic CNVs (12 individuals, lower panel). Primary diagnosis, GD description and values for IQ, Internalizing Problems and GEC scores are listed.

Primary Diagnosis	GD	IQ Score	Internalizing Problems Score	GEC Score
Hemolytic uremic syndrome	1q21.1 deletion	76	65	53
Focal segmental glomerulosclerosis	1q21.1 duplication	78	63	68
Reflux nephropathy	1q21.1 duplication	84	67	83
Aplastic/hypoplastic/dysplastic kidneys	2q13 homozygous deletion (NPHP1)	110	50	59
Chronic glomerulonephritis	2q13 homozygous deletion (NPHP1)	104	52	50
Aplastic/hypoplastic/dysplastic kidneys	Wolf-Hirschhorn syndrome deletion	77	NA	70
Membranous nephropathy	15q24 BP0-BP1 deletion (BBS4, PMI1)	54	62	NA
Aplastic/hypoplastic/dysplastic kidneys	16p11.2 deletion	113	52	73
Obstructive uropathy	16p11.2 deletion	78	52	68
Aplastic/hypoplastic/dysplastic kidneys	17p12 deletion (HNPP)	88	69	64
Cystinosis	CTNS homozygous deletion	91	54	62
Cystinosis	CTNS homozygous deletion	100	56	49
Cystinosis	CTNS homozygous deletion	109	43	40
Aplastic/hypoplastic/dysplastic kidneys	RCAD deletion	70	58	45
Aplastic/hypoplastic/dysplastic kidneys	RCAD deletion	90	87	63
Glomerular, other	RCAD deletion	90	68	72
Aplastic/hypoplastic/dysplastic kidneys	Triple X syndrome	81	63	69
Polycystic kidney disease (Autosomal recessive)	Triple X syndrome	NA	59	NA
Reflux nephropathy	Triple X syndrome	55	59	NA
Reflux nephropathy	2p11.2 deletion	98	NA	54
Obstructive uropathy	2q21.1 duplication	98	71	55
Obstructive uropathy	2q31.1 duplication	100	57	47
Non-Glomerular, other	2q34 deletion	76	61	55
Obstructive uropathy	4p15.2 dupliccation	98	63	77
Aplastic/hypoplastic/dysplastic kidneys	5q35.1 deleton	78	55	72
Focal segmental glomerulosclerosis	9q34.3 duplication	60	NA	66
Chronic glomerulonephritis	10q11.22-q11.23 deletion	96	55	70
Focal segmental glomerulosclerosis	12p13.33-p13.31 deletion, 12q24.33 duplication, 12q24.33 deletion	94	53	58
Non-Glomerular, other	15q21.3 duplication	90	71	62
Reflux nephropathy	16q24.1 duplication	99	48	37
Obstructive uropathy	18q21.33-q22.1 deletion	93	61	67

	Likely Pathogenic CNV carriers			Known Genomic Disorder Carriers							
	N	Mean	s.d.	N	Mean	s.d.	% difference	t test P-value	U test P-Value	pooled s.d.	Cohen's d
IQ Score	12	90.00	12.34	18	86.00	17.14	-4.44	0.46	0.43	15.43	-0.26
Internal. Prob. Score	10	59.50	7.47	18	59.94	9.73	0.75	0.89	0.98	9.01	0.05
GEC Score	12	60.00	11.32	16	61.75	11.62	2.92	0.69	0.71	11.50	0.15
Achievement Score	10	84.20	8.55	14	84.07	24.53	-0.15	0.99	0.75	19.63	-0.01
Externalizing Prob. Score	10	50.30	9.93	18	53.39	10.16	6.14	0.44	0.36	10.08	0.31
Behavioral Sympt. Score	10	53.70	11.72	18	57.50	9.84	7.08	0.40	0.29	10.53	0.36
Adapting Score	10	42.70	12.34	18	42.11	8.79	-1.38	0.90	0.90	10.16	-0.06

Supplementary Table 2. There were no significant differences in NC outcome variables between carriers of Known Genomic Disorders and carriers of Likely Pathogenic CNVs.

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