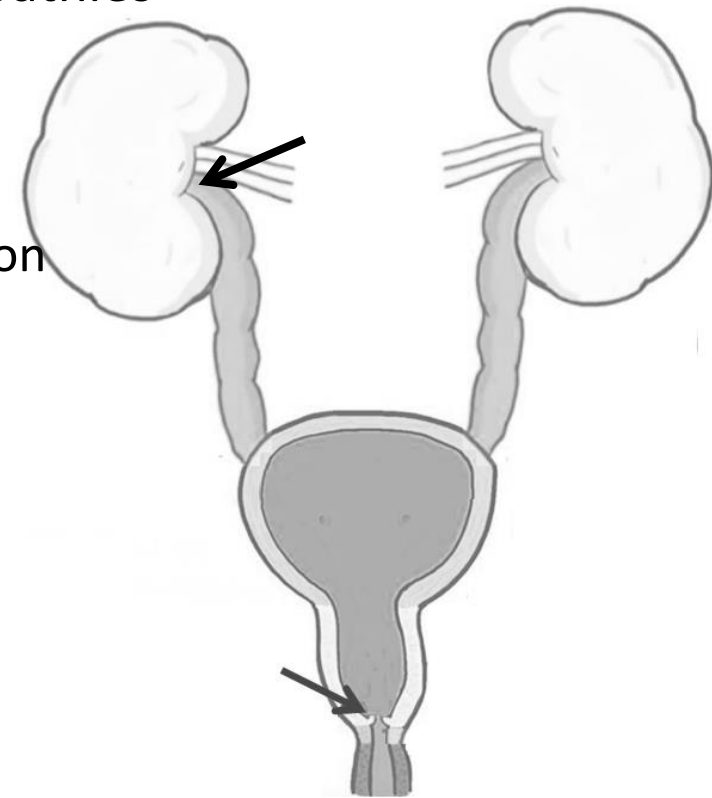


GWAS identifies *CDH12* as candidate gene for kidney injury in posterior urethral valves

Loes F.M. van der Zanden
Radboudumc, Nijmegen, The Netherlands

Posterior urethral valves

- PUV and UPJO: congenital obstructive uropathies
 - PUV: valves in urethra of boys
 - Causes pressure on kidneys
 - May impair kidney development
 - UPJO: obstruction at uretero-pelvic junction
- GWAS to identify genetic variants associated with kidney injury





AGORA data- and biobank

Aetiologic Research into Genetic and Occupational /
Environmental Risk factors for Anomalies in Children

Routine inclusion in Radboudumc Amalia children's hospital

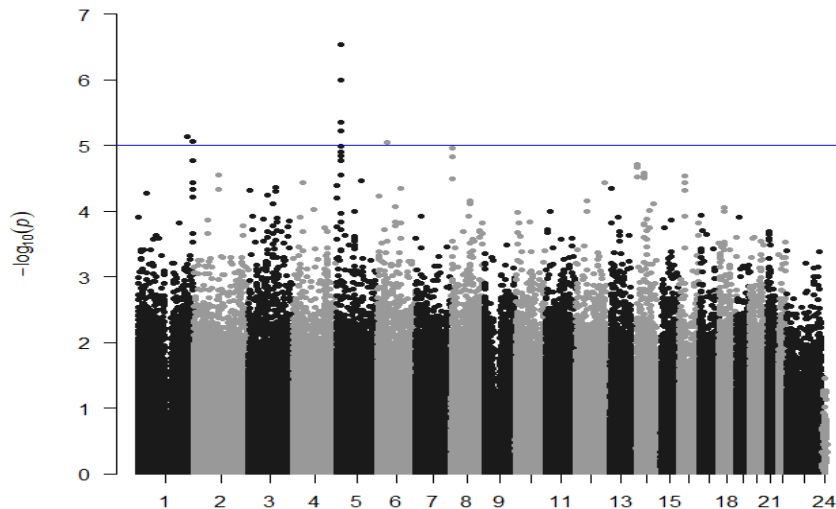
- Clinical data (medical files)
- DNA (blood or saliva)
- Questionnaires from parents
 - *Demographics*
 - *Family history*
 - *Health and lifestyle during pregnancy*





Methods and results GWAS

- Medical files -> signs of kidney injury
 - Dialysis
 - Nephrectomy
 - Transplantation
 - eGFR < 60 ml/min/1.73m²
 - High blood pressure
 - Antihypertensive medication
 - Proteinuria
 - One kidney < 45%



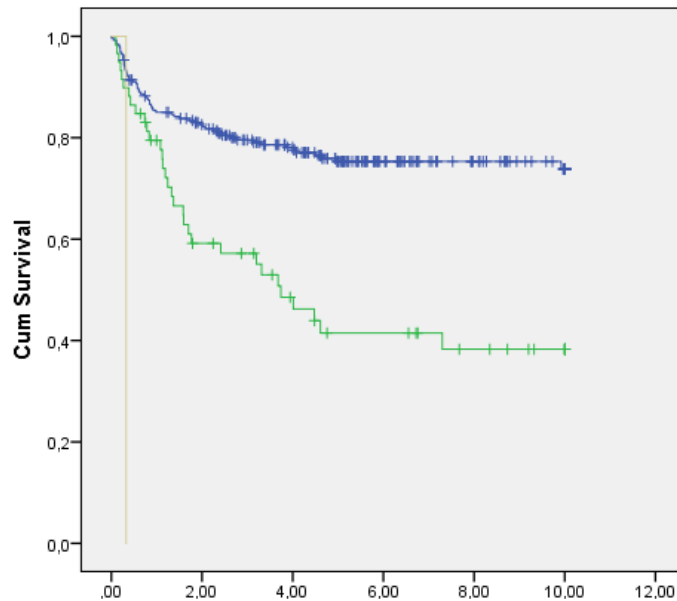
- 357 patients
 - 141 kidney injury within 5 years
 - 216 no kidney injury
- Manhattan plot
 - Peak on chromosome 5



Results survival analyses - discovery

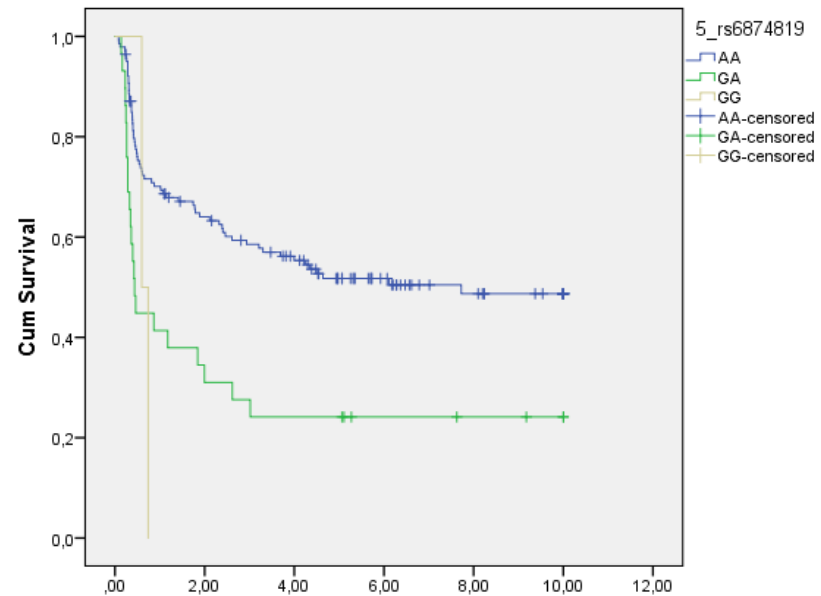
PUV

316 PUV, 93 kidney injury



UPJO

171 UPJO, 90 kidney injury



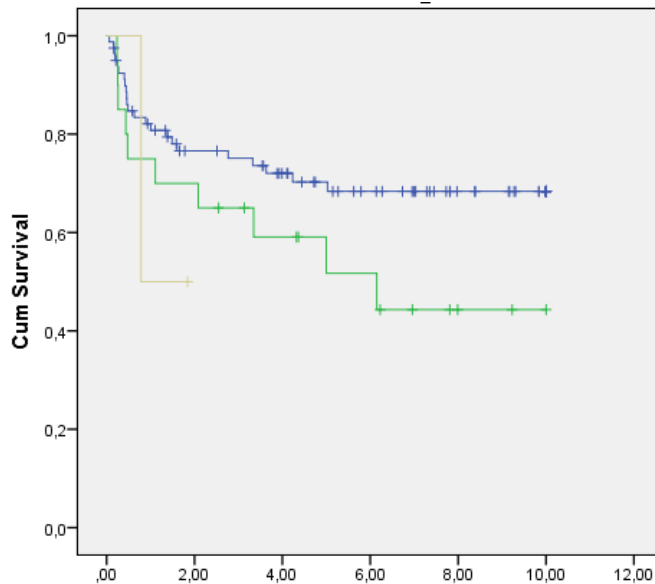
	PUV patients		UPJO patients	
Genotype	HR (95%CI)	P	HR (95%CI)	P
AA	ref	ref	ref	ref
GA	2.8 (1.8-4.3)	$3 \cdot 10^{-6}$	2.4 (1.5-3.8)	0.001
GG	18 (2.4-131)	0.005	3.0 (0.7-13)	0.12



Results Dutch replication

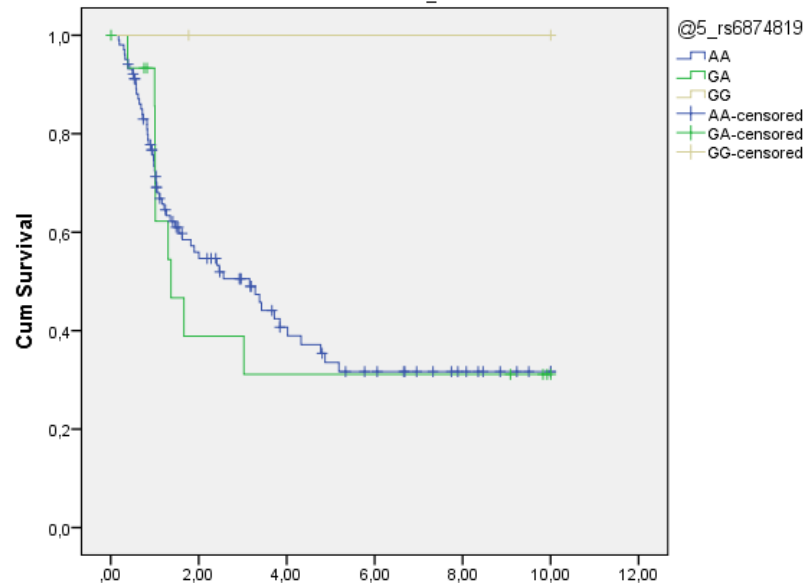
PUV

102 PUV, 34 kidney injury



UPJO

120 UPJO, 65 kidney injury



@5_rs6874819
 AA
 GA
 GG
 AA-censored
 GA-censored
 GG-censored

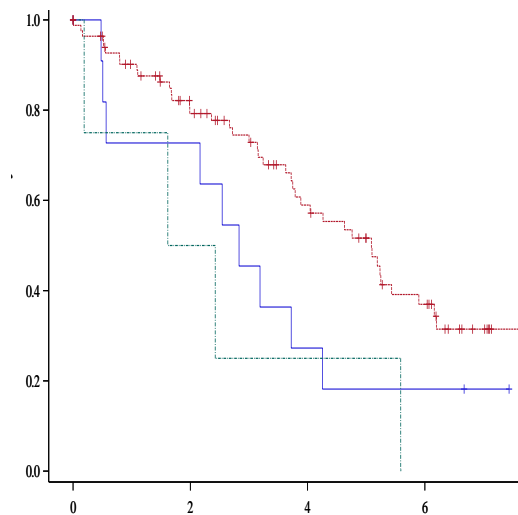
	PUV patients		UPJO patients	
Genotype	HR (95%CI)	P	HR (95%CI)	P
AA	ref	ref	ref	ref
GA	1.8 (0.9-3.8)	0.11	1.1 (0.5-2.2)	0.84
GG	2.4 (0.3-18)	0.40	-	-

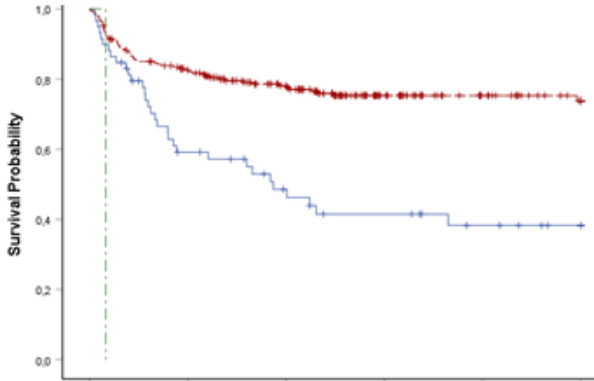


Results European replication

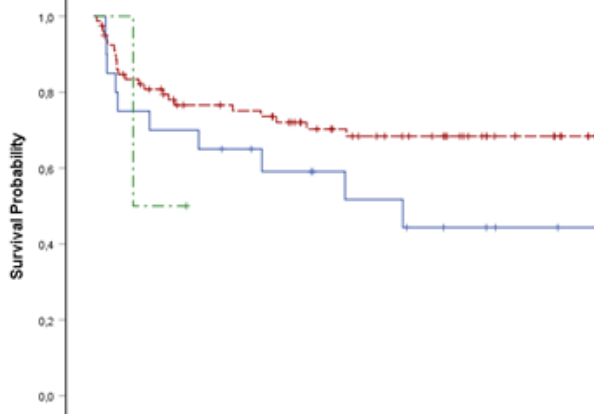
- Replication in 102 European PUV patients
- Different endpoint: Kidney 'death'
 - Dialysis / kidney transplantation
 - eGFR > 50% ↓
 - eGFR < 10

European PUV patients		
Genotype	HR (95%CI)	P
AA	ref	ref
GA	1.8 (0.9-3.9)	0.11
GG	3.1 (1.1-9.1)	0.04

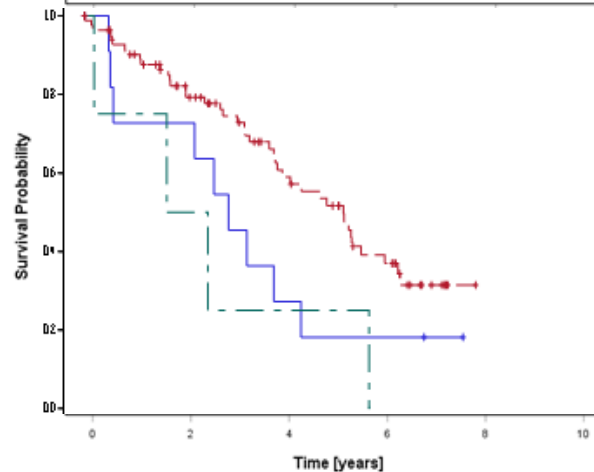




	Discovery	
Genotype	HR (95%CI)	P
AA	Ref	ref
GA	2.8 (1.8-4.3)	3×10^{-6}
GG	18 (2.4-131)	5×10^{-3}



	Dutch replication	
Genotype	HR (95%CI)	P
AA	ref	ref
GA	1.8 (0.9-3.8)	0.11
GG	2.4 (0.3-18)	0.40

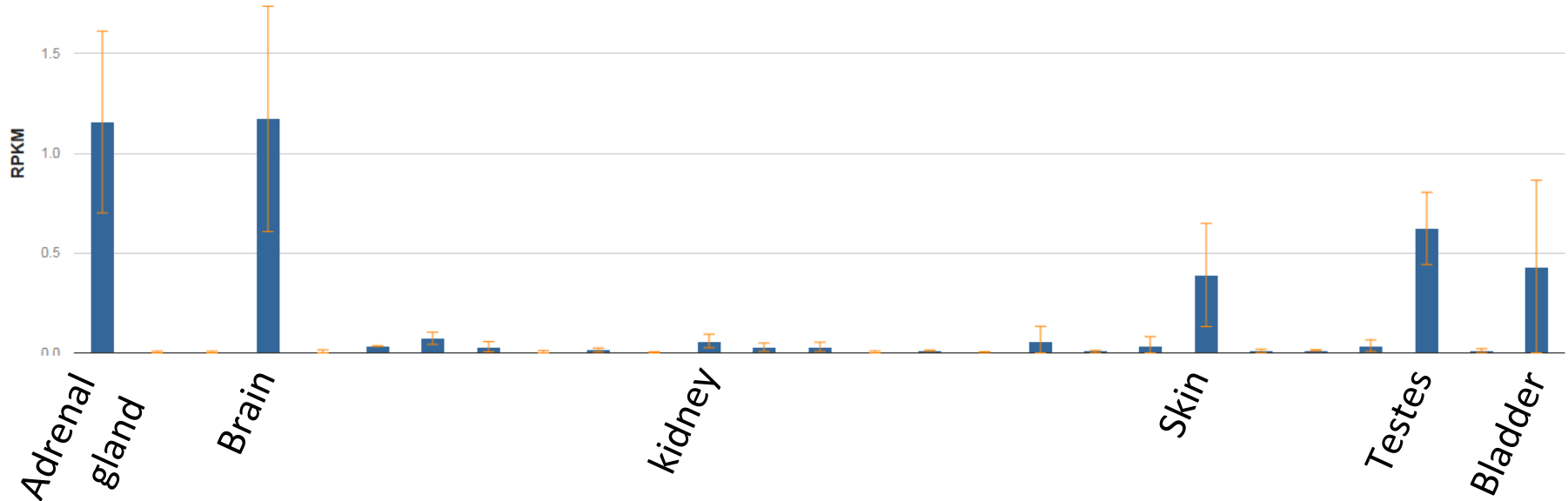


	European replication	
Genotype	HR (95%CI)	P
AA	ref	ref
GA	1.8 (0.9-3.9)	0.11
GG	3.1 (1.1-9.1)	0.04



CDH12 - function and expression

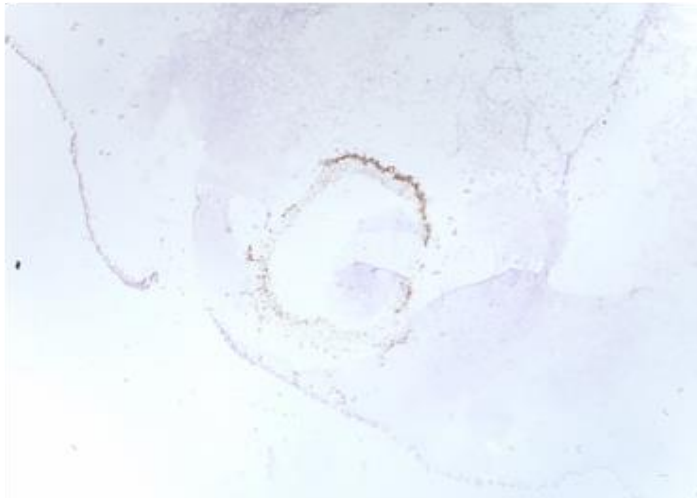
- SNP in intron of *CDH12*
 - Member of gene family of adhesion receptors
 - Cell recognition and sorting
 - Not described in relation to kidney development



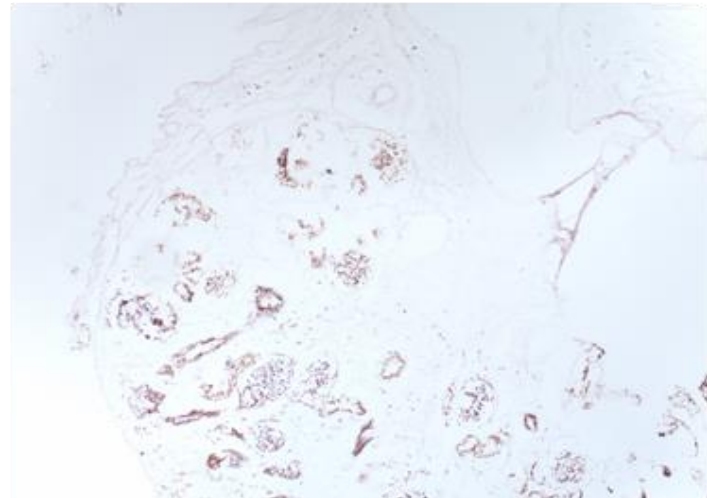
CDH12 - expression in fetal tissues

- Study showed expression of *CDH12* in fetal kidney
 - We confirmed this (brain, adult and fetal kidney)
 - Transcriptomic analyses in 15 fetal tissues -> 2nd highest in kidney

retina

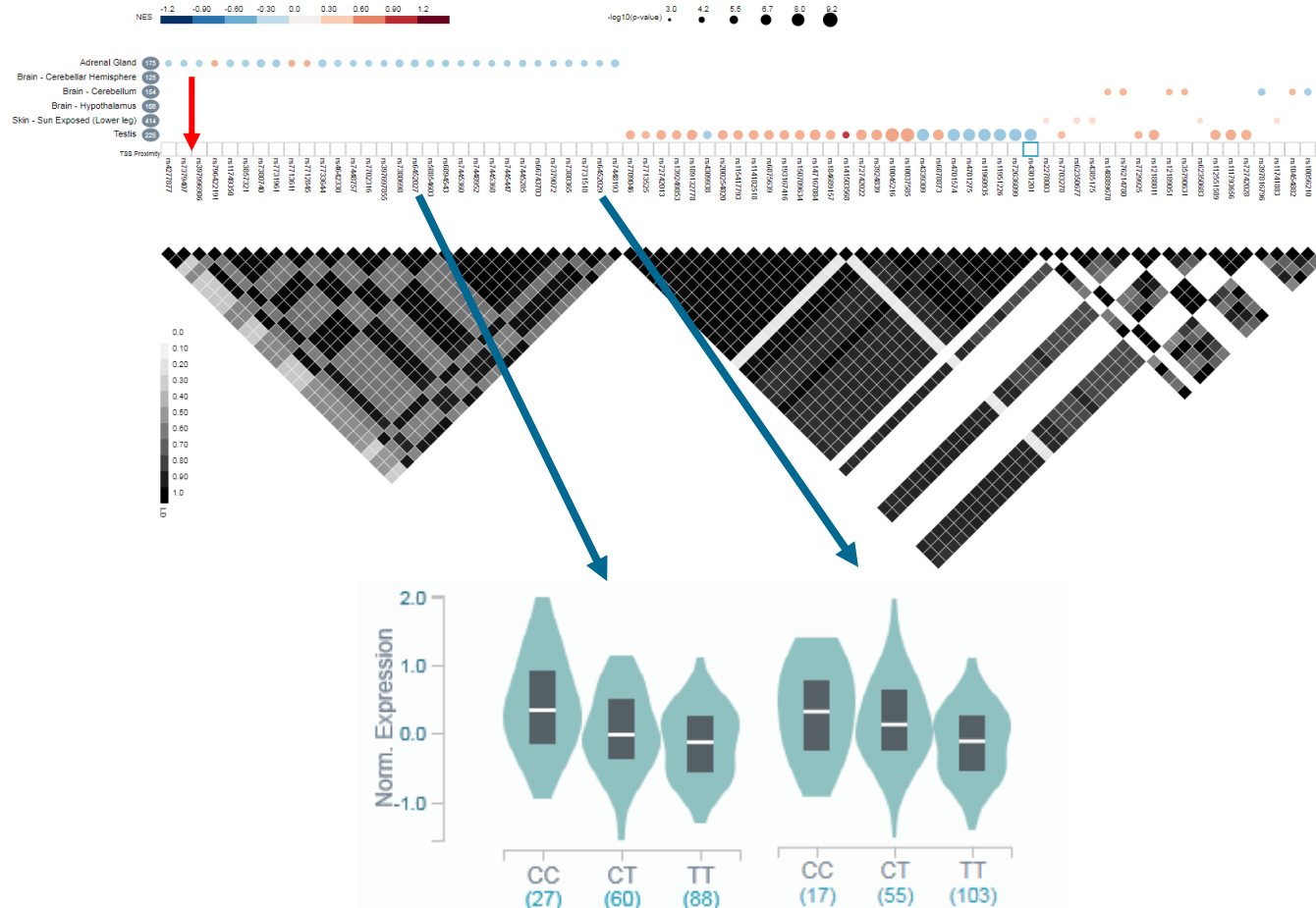


12 wpc





CDH12 - GTEx portal





CDH12 - possible mechanism

- *CDH12* not described in relation to kidney development

PUV



- Future research
 - ✓ Role of CDH12 in monocyte infiltration
 - ✓ Role of CDH12 in progression of obstructive nephropathy
 - ✓ Prognostic value of *CDH12* variants in PUV patients



Acknowledgements

- Radboudumc
 - Prof. Wout Feitz
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 - Dr. Martijn Steffens
 - Dr. Josine Quaedackers
- European replication (4C study)
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- Transcriptome atlas of organogenesis
 - Prof. Neil Hanley
- Expression studies
 - Prof. Paul Winyard

