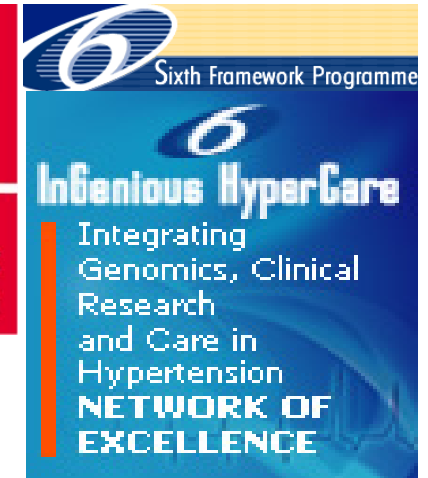


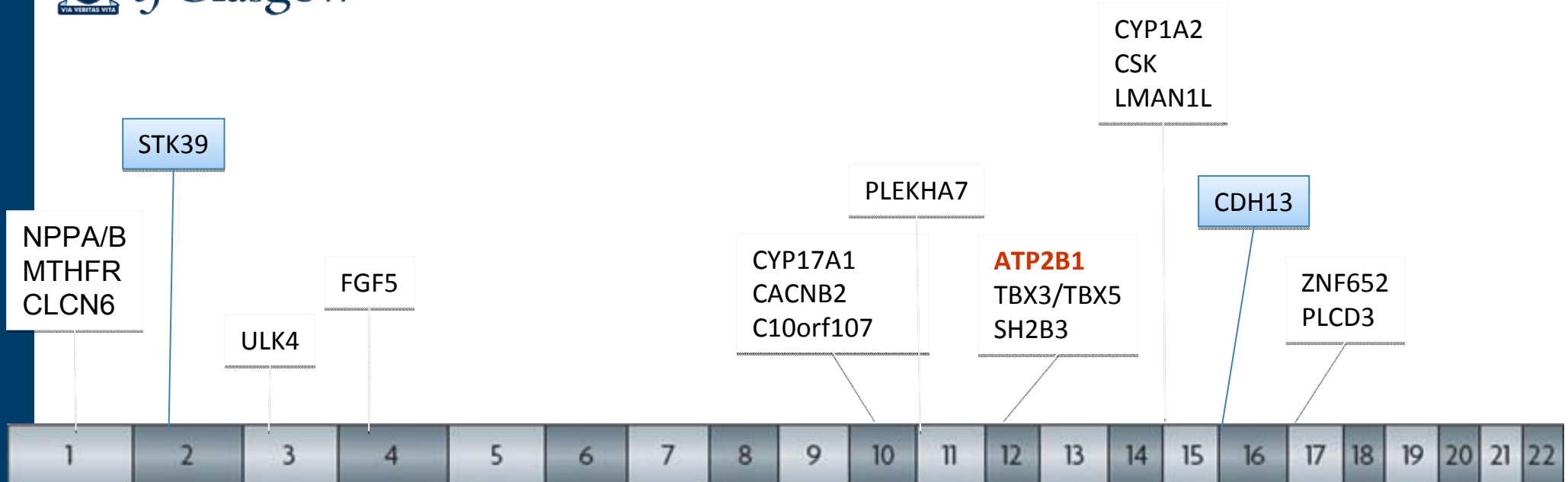


ISTITUTO AUXOLOGICO ITALIANO
Istituto di Ricovero e Cura a Carattere Scientifico



InGenious HyperCare genome-wide-association study of blood pressure extremes – Preliminary results

Sandosh Padmanabhan, Olle Melander, Toby Johnson, Anna Maria Di Blasio, Wai K Lee, Davide Gentilini, Claire E. Hastie, Cristina Menni, Maria Cristina Monti, Christian Delles, Stewart Laing, Barbara Corso, Gerjan Navis, Arjan Kwakernaak, Pim van der Harst, Murielle Bochud, Marc Maillard, Michel Burnier, Thomas Hedner, Sverre Kjeldsen, Björn Wahlstrand, Marketa Sjögren, Cristiano Fava, Martina Montagnana, Elisa Danese, Ole Torffvit, Bo Hedblad, Harold Snieder, John M.C. Connell, Morris Brown, Nilesh J. Samani, Martin Farrall, Giancarlo Cesana, Giuseppe Mancia, Stefano Signorini, Guido Grassi, Susana Eyheramendy, H. Erich Wichmann, Maris Laan, David P Strachan, Peter Sever, Denis Shields, Alice Stanton, Peter Vollenweider, Alexander Teumer, Henry Völzke, Rainer Rettig, Christopher Newton-Cheh, Pankaj Arora, Feng Zhang, Nicole Soranzo, Tim Spector, Gavin Lucas, Sekar Kathiresan, David Siscovick, Jian'an Luan, Ruth J.F. Loos, Nicholas J. Wareham, Brenda W. Penninx, Ilja M. Nolte, Martin McBride, William H. Miller, Stuart A Nicklin, Andrew H Baker, Delyth Graham, Robert A McDonald, Jill Pell, Naveed Sattar, Paul Welsh, Patricia B. Munroe, Mark Caulfield, Alberto Zanchetti, Anna F Dominiczak.



Meta-analysis of quantitative SBP and DBP

Global BPgen - stage 1 – n= 34,433, validation n=71 225 Europeans

CHARGE – n= 29,136

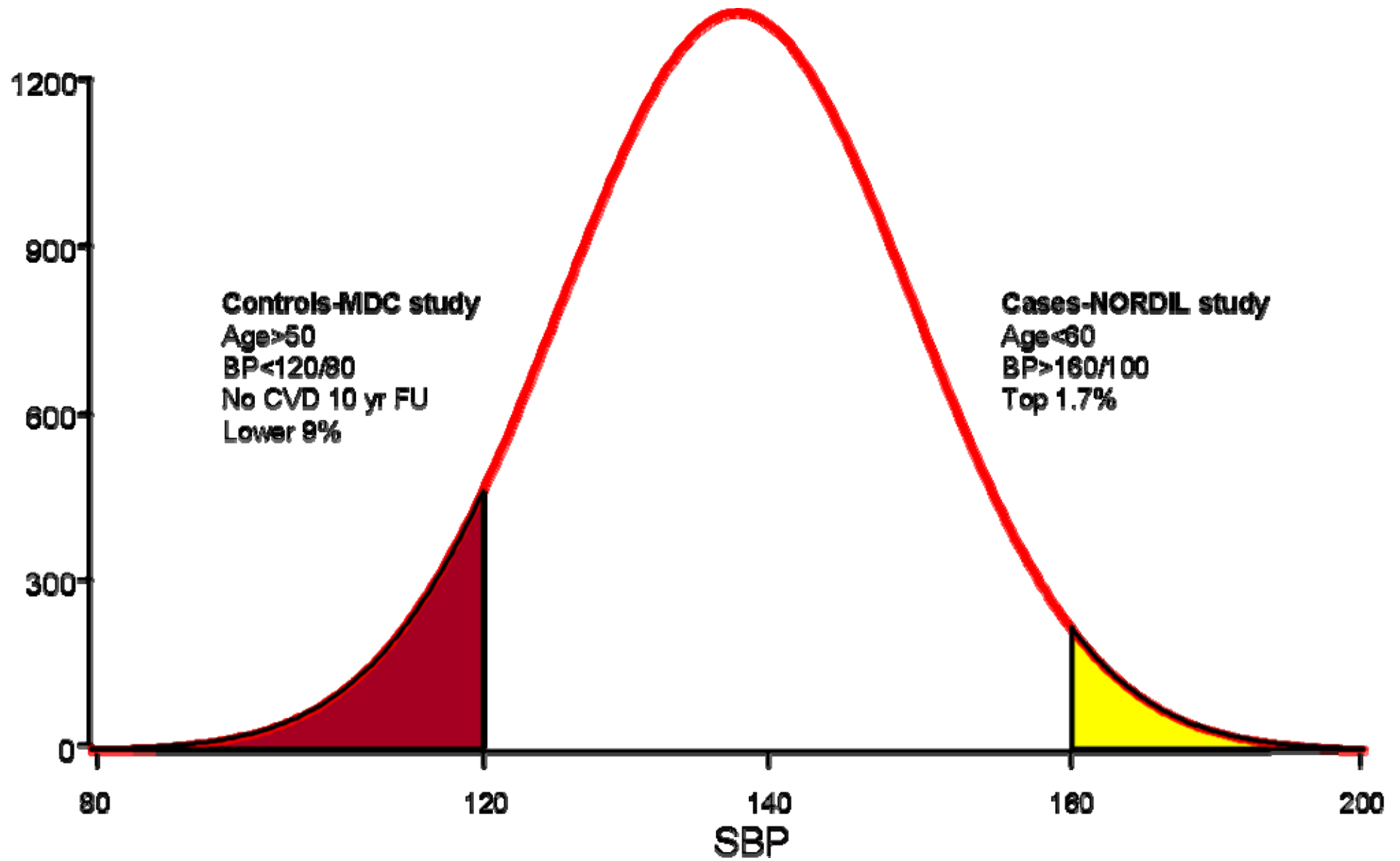
Together these explain <1% of the population variation in BP

Newton-Cheh C et al. Nat Genet 2009;41:666–676.

Levy D et al. Nat Genet 2009; 41:677–687.

Wang Y et al. Proc Natl Acad Sci 2009; 106:226–231

Org E et al. Hum Mol Genet 2009, 18:2288–2296.



Illumina 550K Single and Illumina 610 Quad V1 BeadChip

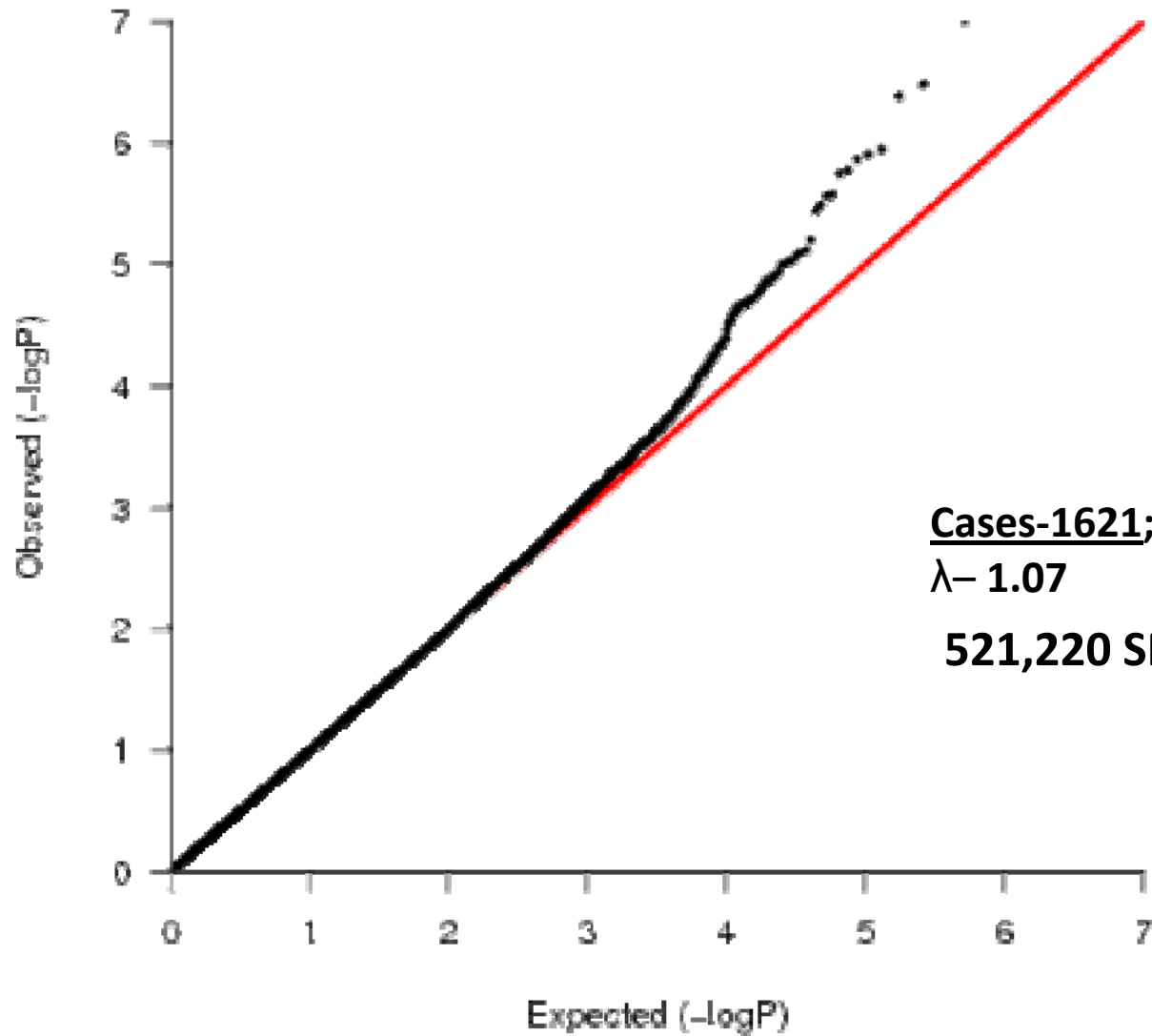
**551,629 SNPs common to both the Single and Quad
chips**

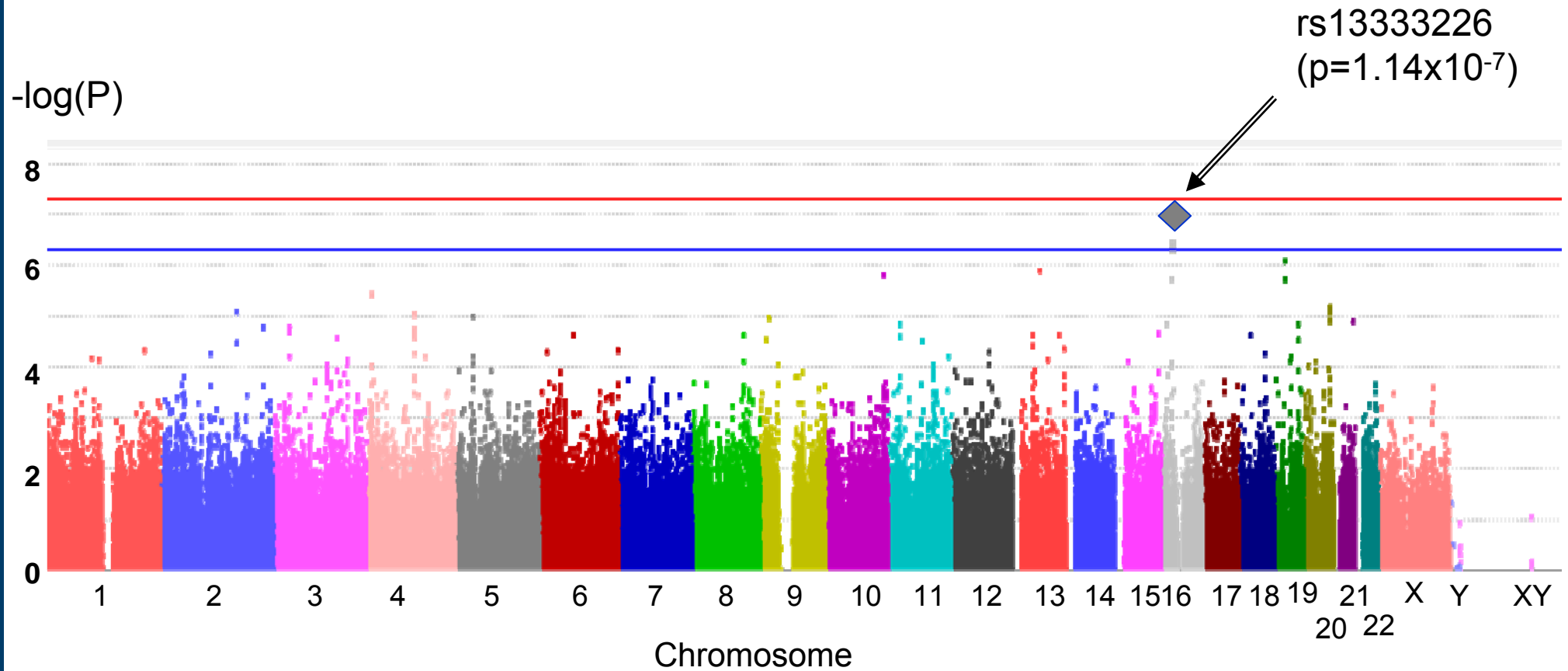
QC –

SNPS $MAF < 1\%$; $HWE < 5 \times 10^{-6}$

Samples – MDS outliers, relatedness, unspecified sex

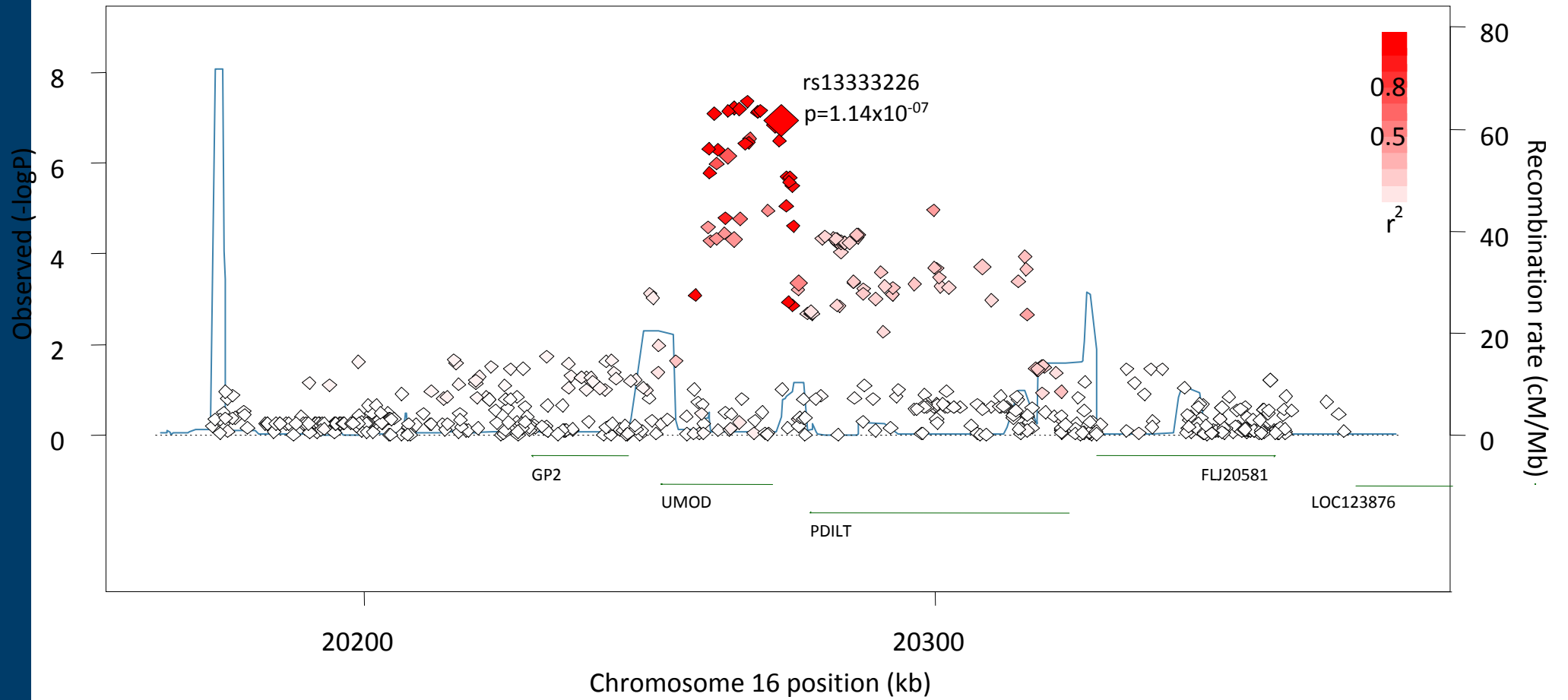
	Controls (n=1699)	Cases (n=1621)
Age at enrolment, years	57.4 (5.9)	55.4 (7.1)
BMI, kg/m ²	24.2 (3.5)	27.1 (7.8)
SBP, mmHg	115.8 (6.8)	175.8 (22.5)
DBP, mmHg	73.7 (5.7)	104.7 (11.8)







rs13333226 region





**Stage 1 samples of the Global BPgen consortium –
n= 34,433**

MONICA/PAMELA – n= 1640

MPP – n= 3013

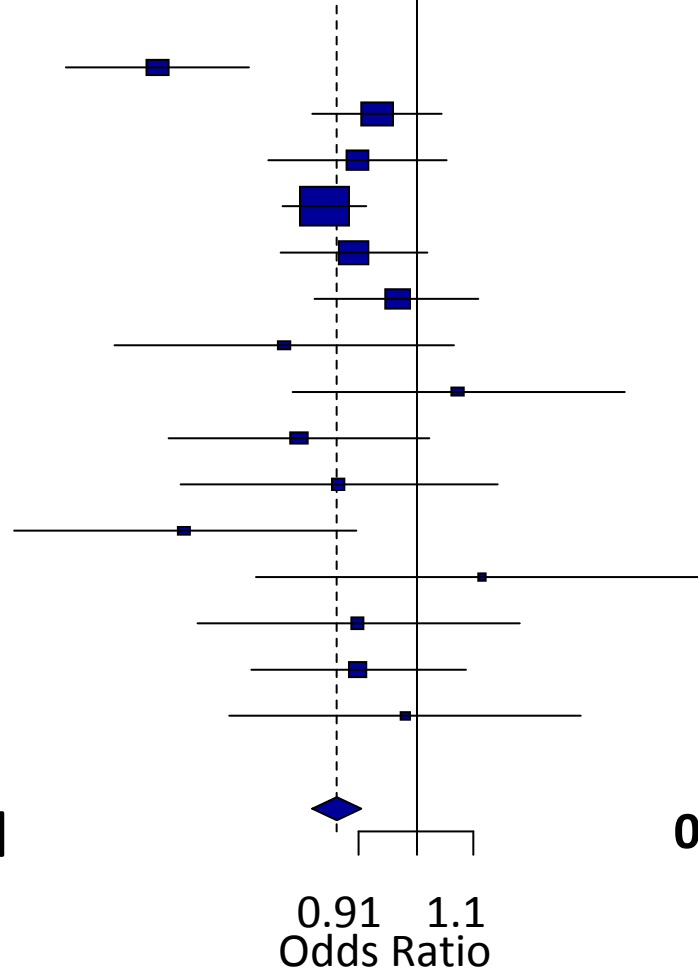
MDC – n=13,868

NESDA – n= 718

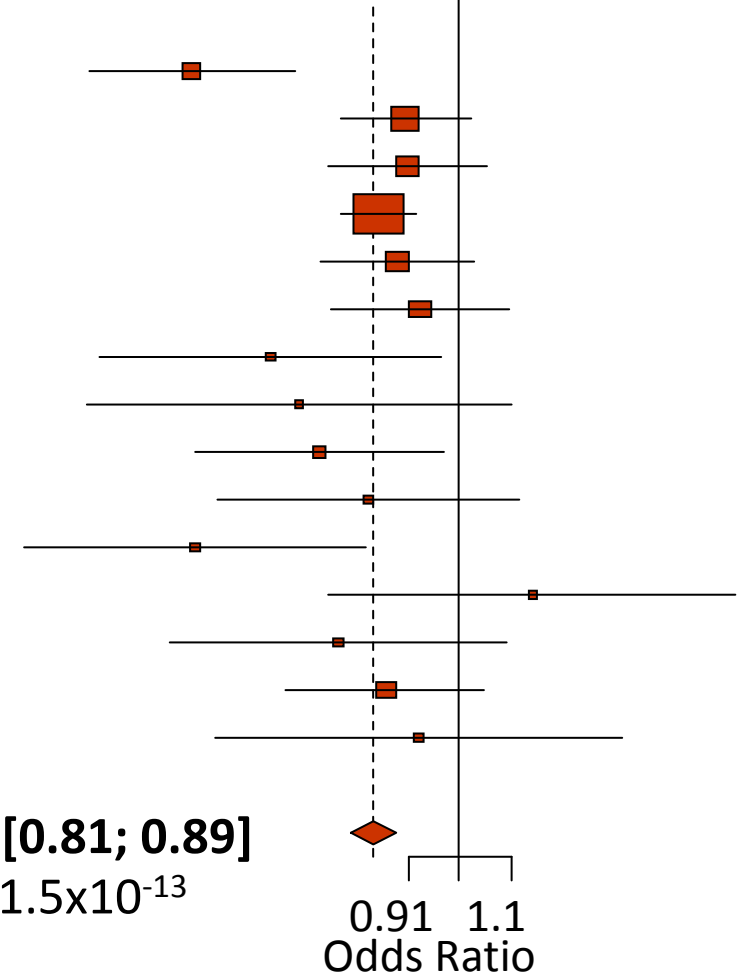
Combined Analysis (incl Discovery) n=39,706

Swedish
BRIGHT/ASCOT
MPP
MDC
PREVEND
CoLaus
KORA
SHIP
B58C
TwinsUK
MIGen
DGI
Fenland
MONICA/PAMELA
NESDA

Unadjusted



Adjusted



Excluding Discovery

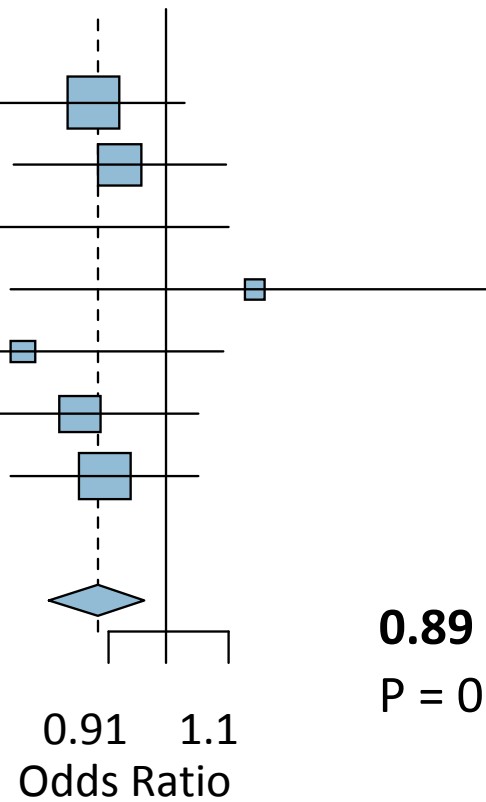
0.89 [0.86-0.93]
P= 7.36×10^{-08}

0.86 [0.83-0.90]
P= 1.61×10^{-10}

Cohorts with eGFR

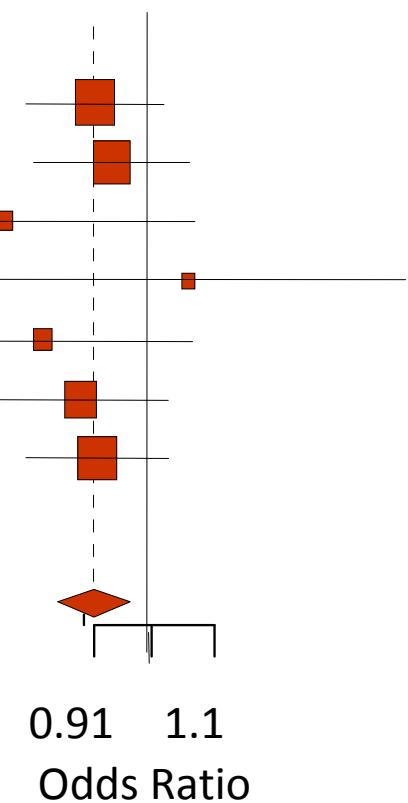
PREVEND
CoLaus
SHIP
DGI
Fenland
MONICA/PAMELA
MPP

0.90 [0.83; 0.97]
P = 0.004



After eGFR adjustment

0.89 [0.83; 0.96]
P = 0.003



Tamm Horsfall protein (THP) / uromodulin
Secreted into urine by cleavage of GPI anchor

Expressed primarily in the thick ascending limb of the loop of Henle (TAL)

Physiological function not well understood

Immunostimulatory

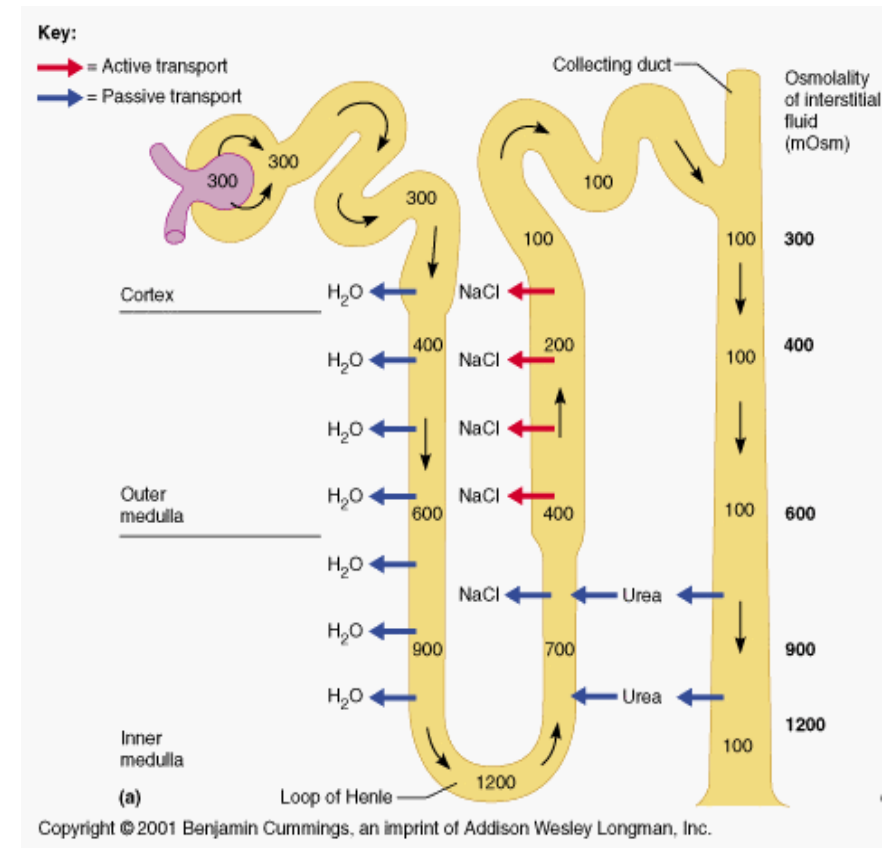
Protective against nephrolithiasis and UTI

Mutations in exons 4 and 5

Familial juvenile hyperuricemic nephropathy

Autosomal-dominant medullary cystic kidney disease [MCKD2]

Glomerulocystic kidney disease (GCKD)



Anatomically normal kidneys

No change in steady state electrolyte concentrations

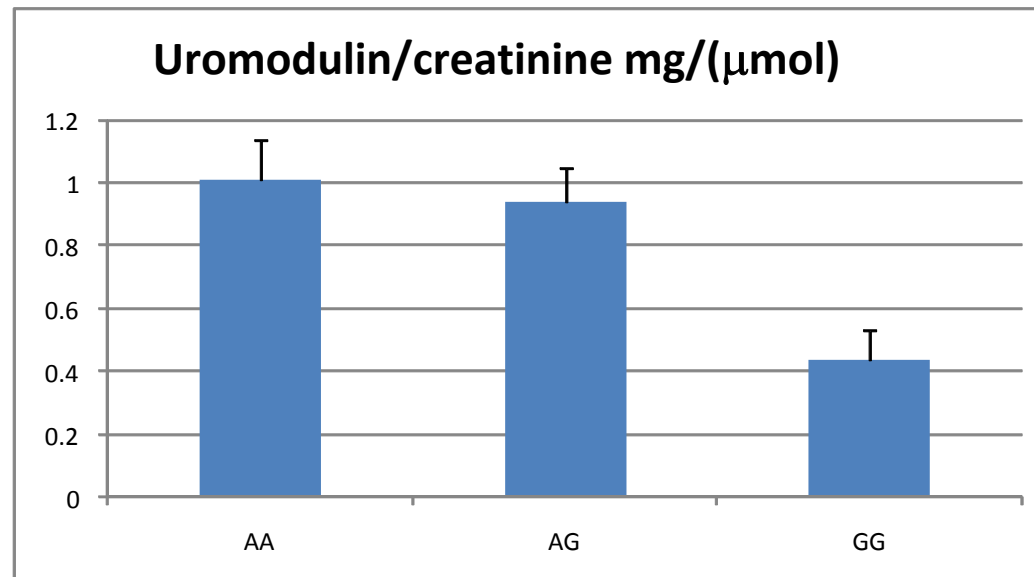
Creatinine clearance 63% lower

**Significant upregulation of the major transporters of the TAL
(including NKCC, ROMK, CIC-Kb and barttin) and DCT
(NCC)**

Juxtaglomerular immunoreactive COX2 decreased

Renin mRNA decreased

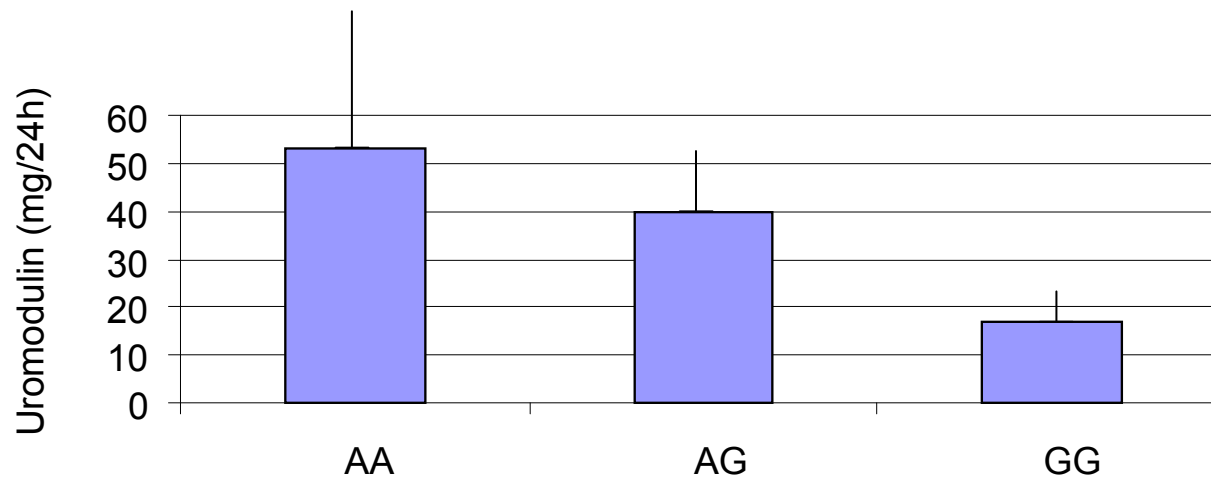
	AA (n=141)	AG (n=93)	GG (n=22)	p-value
Male:Female	0.7	0.8	0.6	0.763
Age (years)	64.7(8.4)	63.9(7.8)	59.5(9.5)	0.036
SBP (mm Hg)	156(19.5)	151.5(18.9)	153.3(14.5)	0.205
DBP (mm Hg)	93.1(10)	90.9(10.7)	93.3(10.3)	0.266
Body mass index (Kg/m ²)	26.8(4.6)	26.8(5.4)	27.2(3.9)	0.927
eGFR (ml/min/1,73m ²)	67.6(16.2)	70.3(12.3)	79.5(15.2)	0.005



P=0.007



	AA (n=52)	AG (n=46)	GG (n=12)	P-value
M / F (n)	28 / 24	18 / 28	7 / 5	0.258
Age (years)	58 (49 - 67)	56 (49 - 66)	59 (49 - 66)	0.889
Body mass index (Kg/m ²)	26.1 (23.6 - 29.3)	24.4 (21.8 - 29)	24.7 (24 - 28)	0.175



P=0.005

First 7 days on a low sodium diet (LS, 50 mmol Na⁺ per day, balance verified by repeated 24h urine)

Second 7 days on a high-sodium diet (HS, 200 mmol Na⁺ per day)

	AA (n=40)	AG (n=19)	GG (n=5)	p-value
Age (years)	26 (8)	23 (6)	23 (4)	0.105
UMOD LS (median (IQR) (mg/L))	10.3 (6.9-15.6)	9.9 (7.4-15.7)	7.0 (2.5-13.3)	0.002
UMOD HS median (IQR) (mg/L)	11.9 (7.5-27.9)	11.6 (11.4-23)	12.2 (6.9-23.6)	0.513

Common variant in UMOD gene associated with HTN

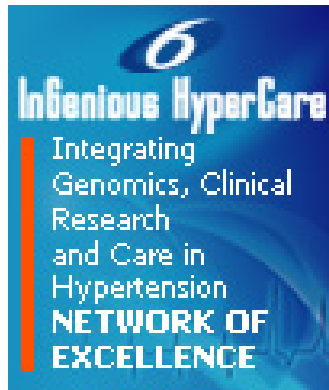
The effect size of the risk allele is comparable to the effect sizes of the previous robust association signals for BP

Potential new pathway of HTN causation possibly through renal salt balance



University
of Glasgow

Acknowledgements



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