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Hypertension genomics metabolomics and big data

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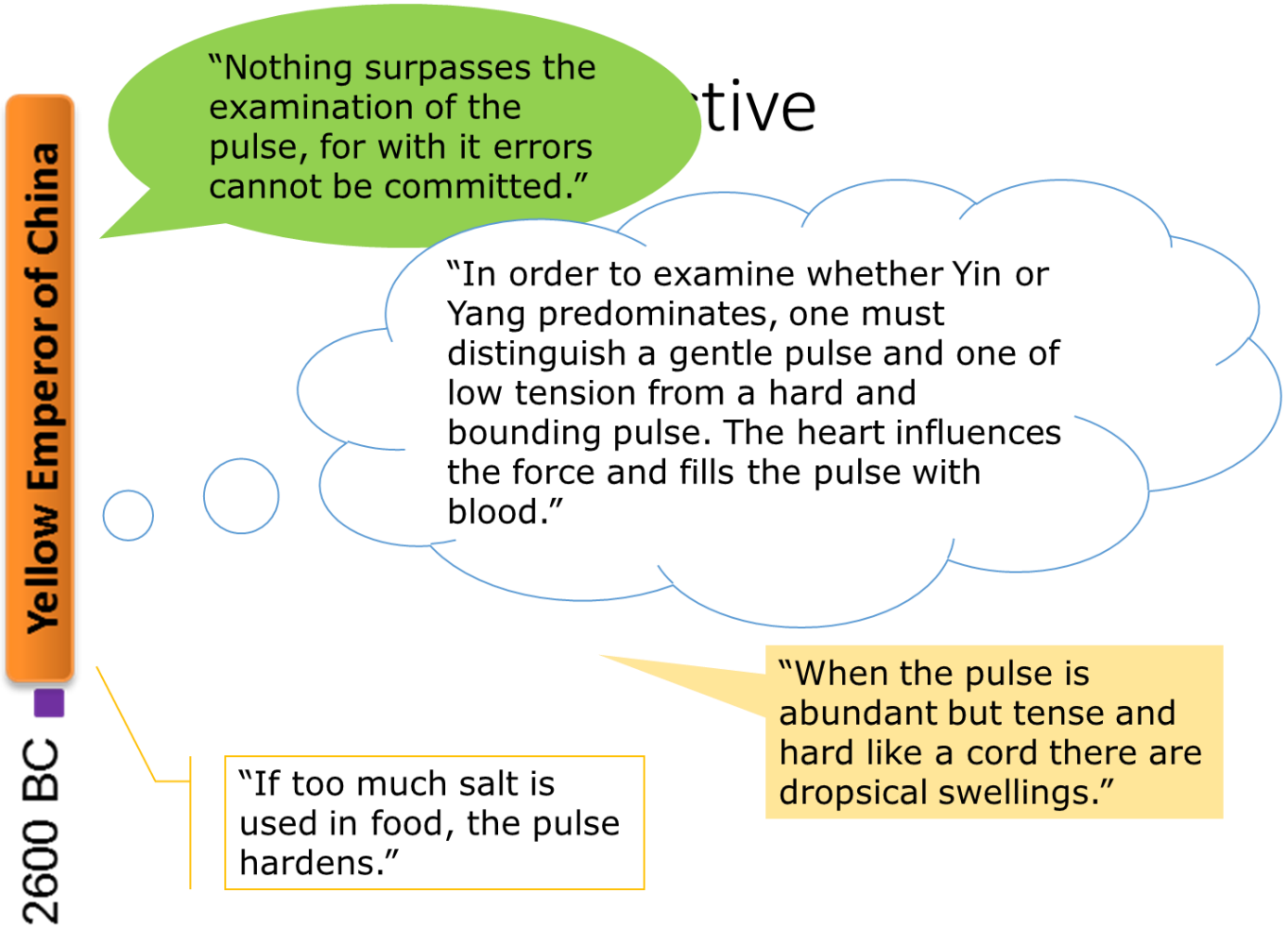
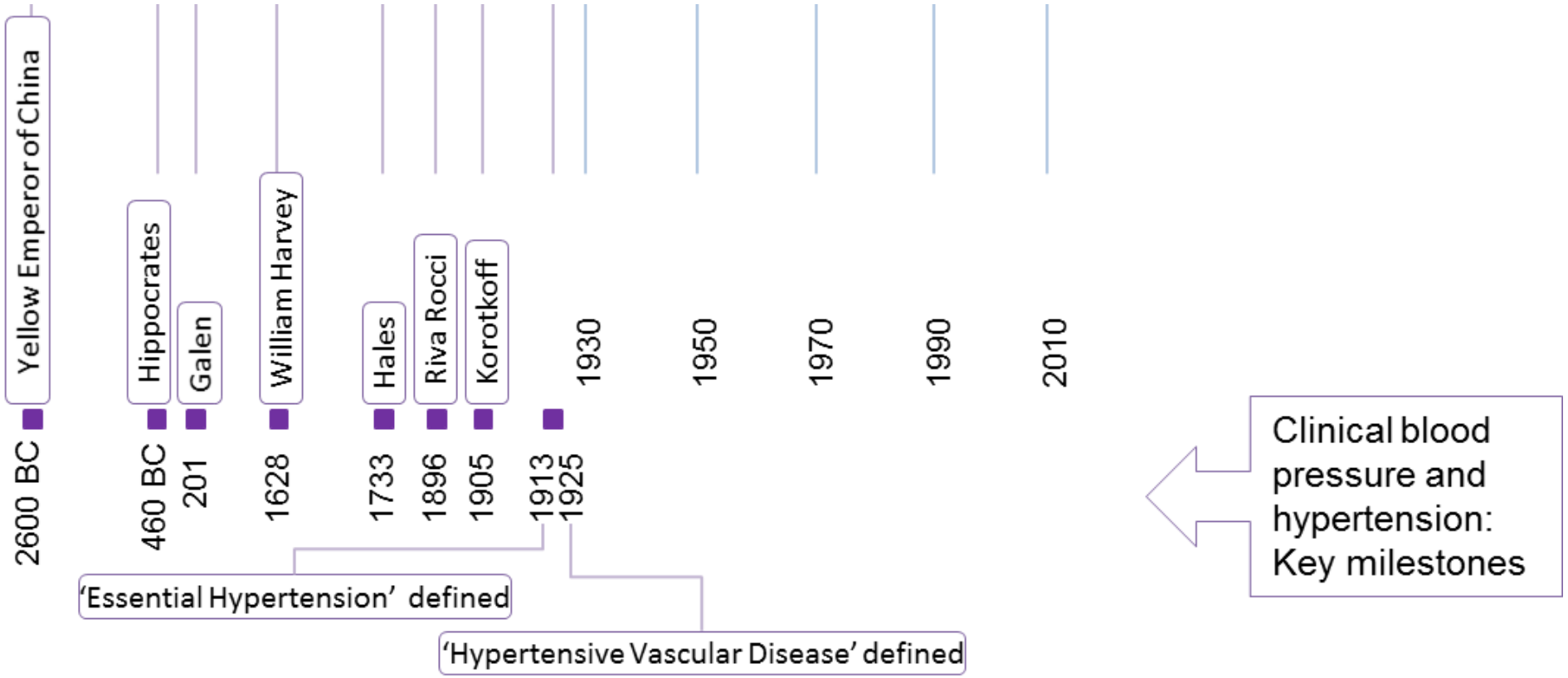
INSPIRING PEOPLE

Historical Perspective



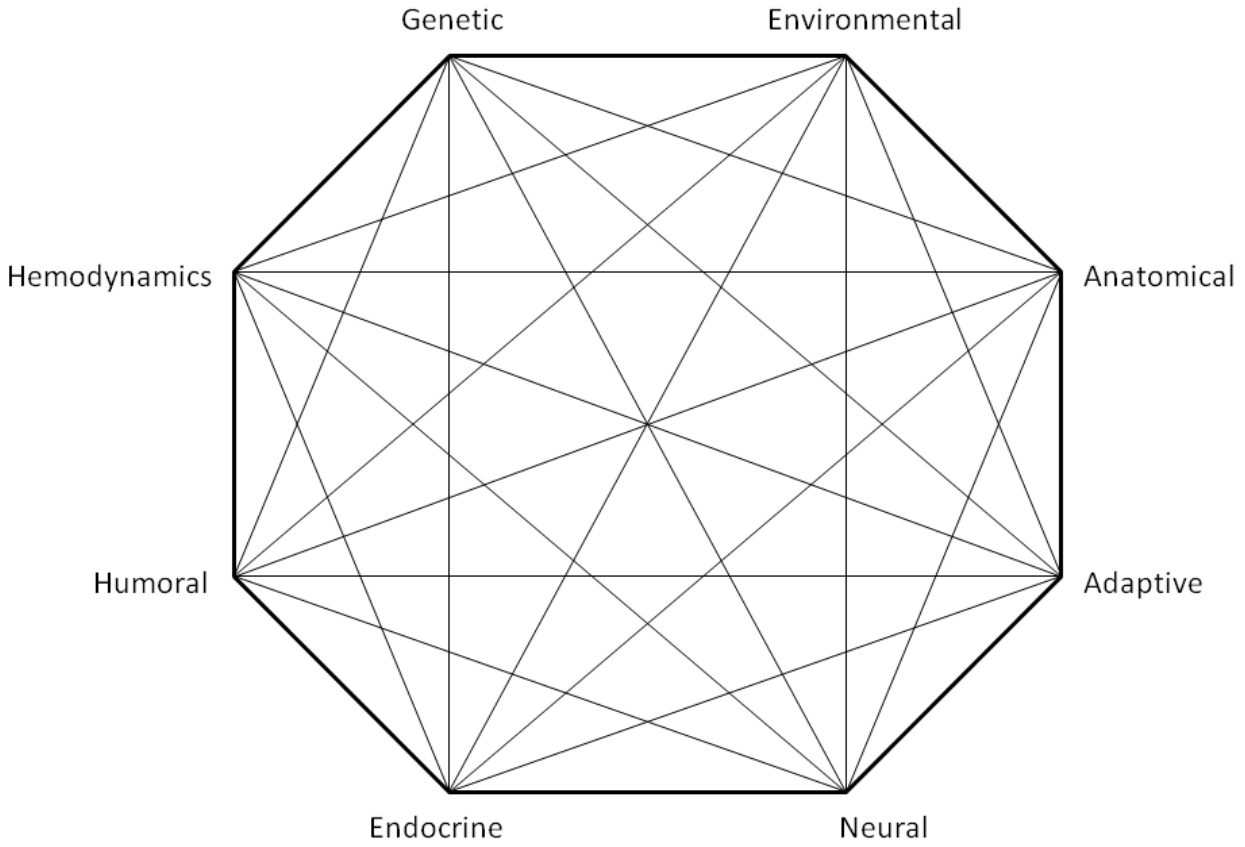
Padmanabhan, Caulfield, Dominiczak. Circ Res. 2015;116(6):937-59.

Historical Perspective



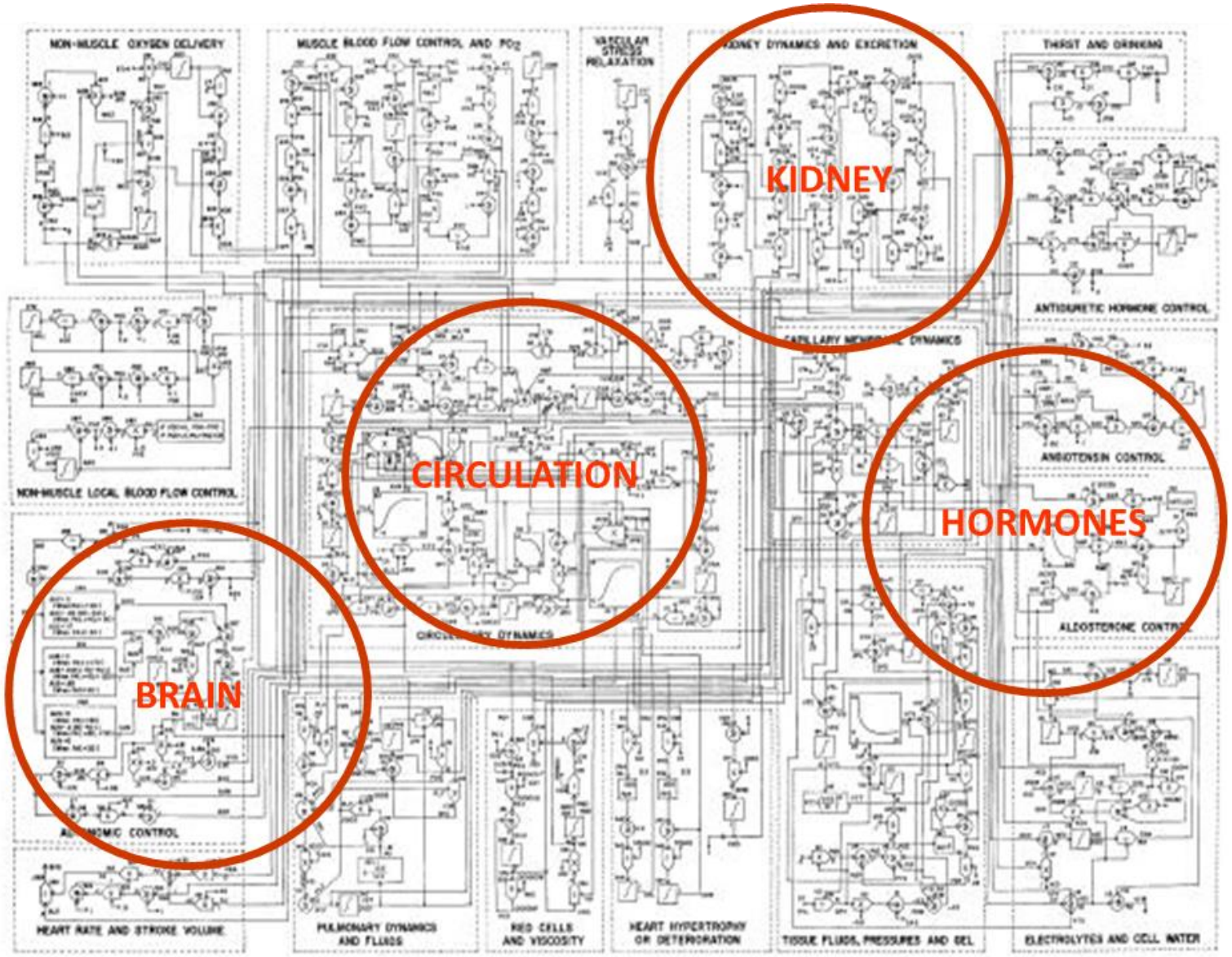
Padmanabhan, Caulfield, Dominiczak. Circ Res. 2015;116(6):937-59.

1960 - Paige Model of Hypertension



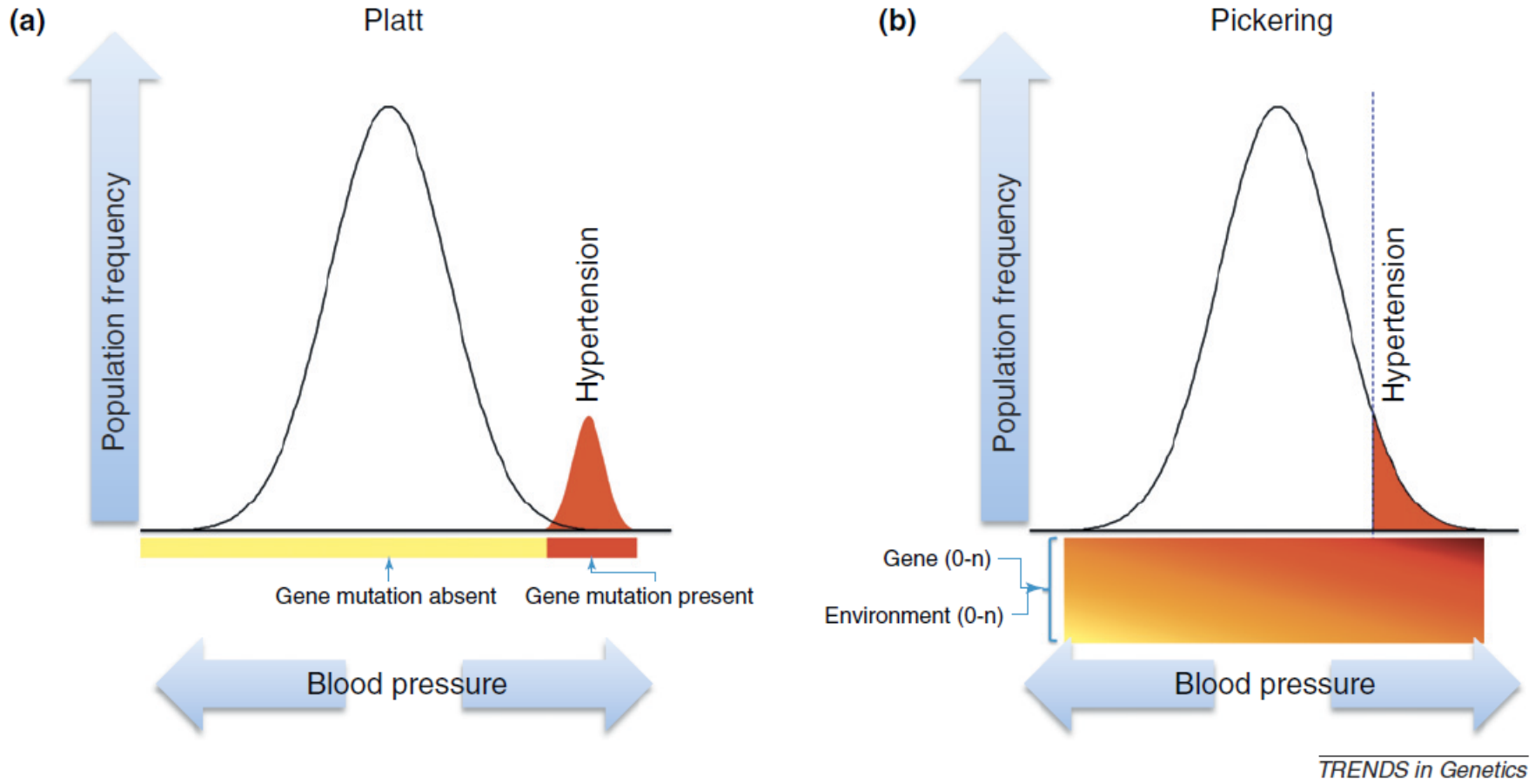
Padmanabhan, Caulfield, Dominiczak. Circ Res. 2015;116(6):937-59.

1972 - Long Term BP Control Model



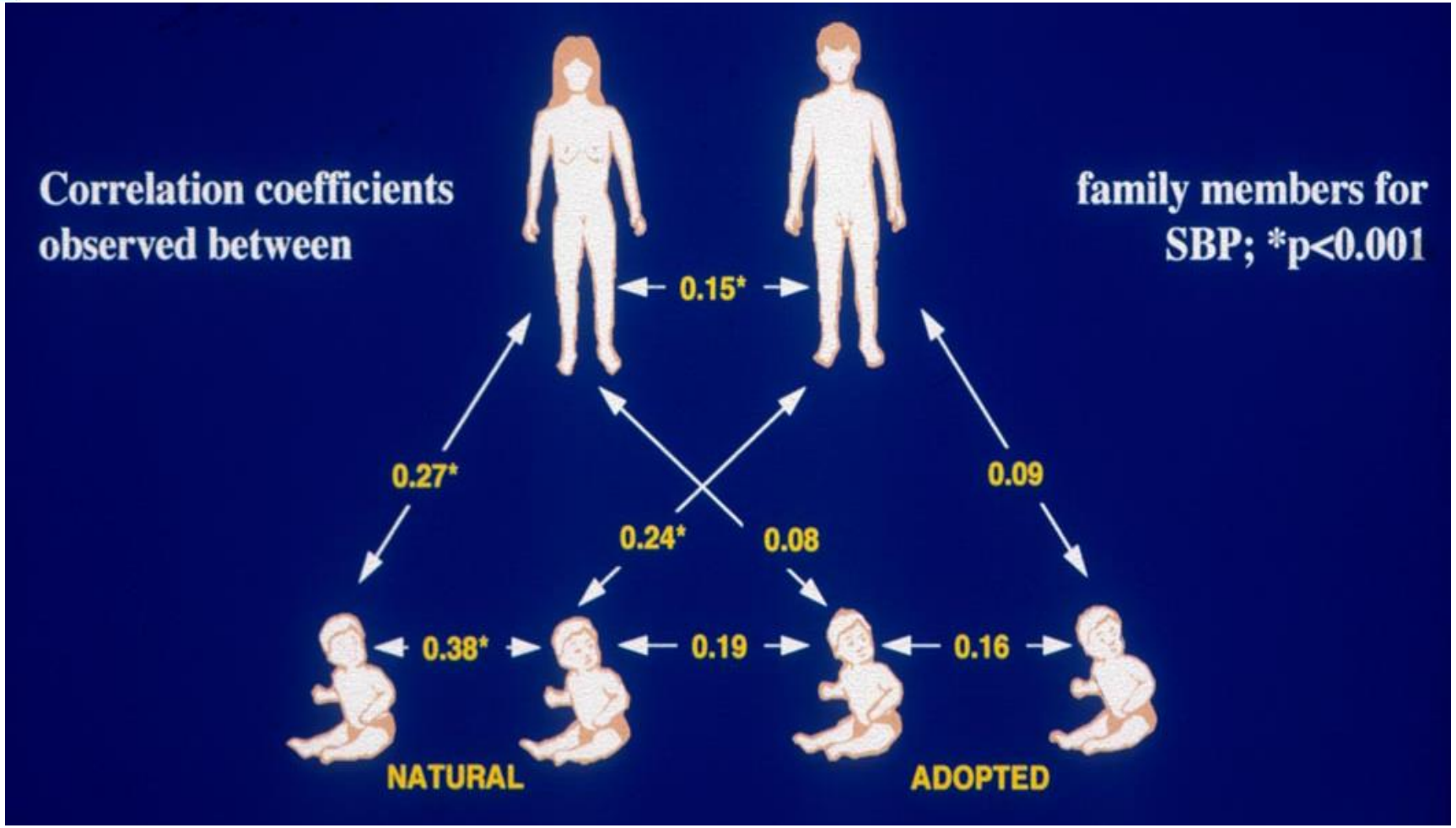
Guyton and Coleman 1972

Platt-Pickering Debate



Padmanabhan et al. Trends Genet. 2012 Aug;28(8):397-408.

Montreal Adoption Study



Mongeau et al 1986

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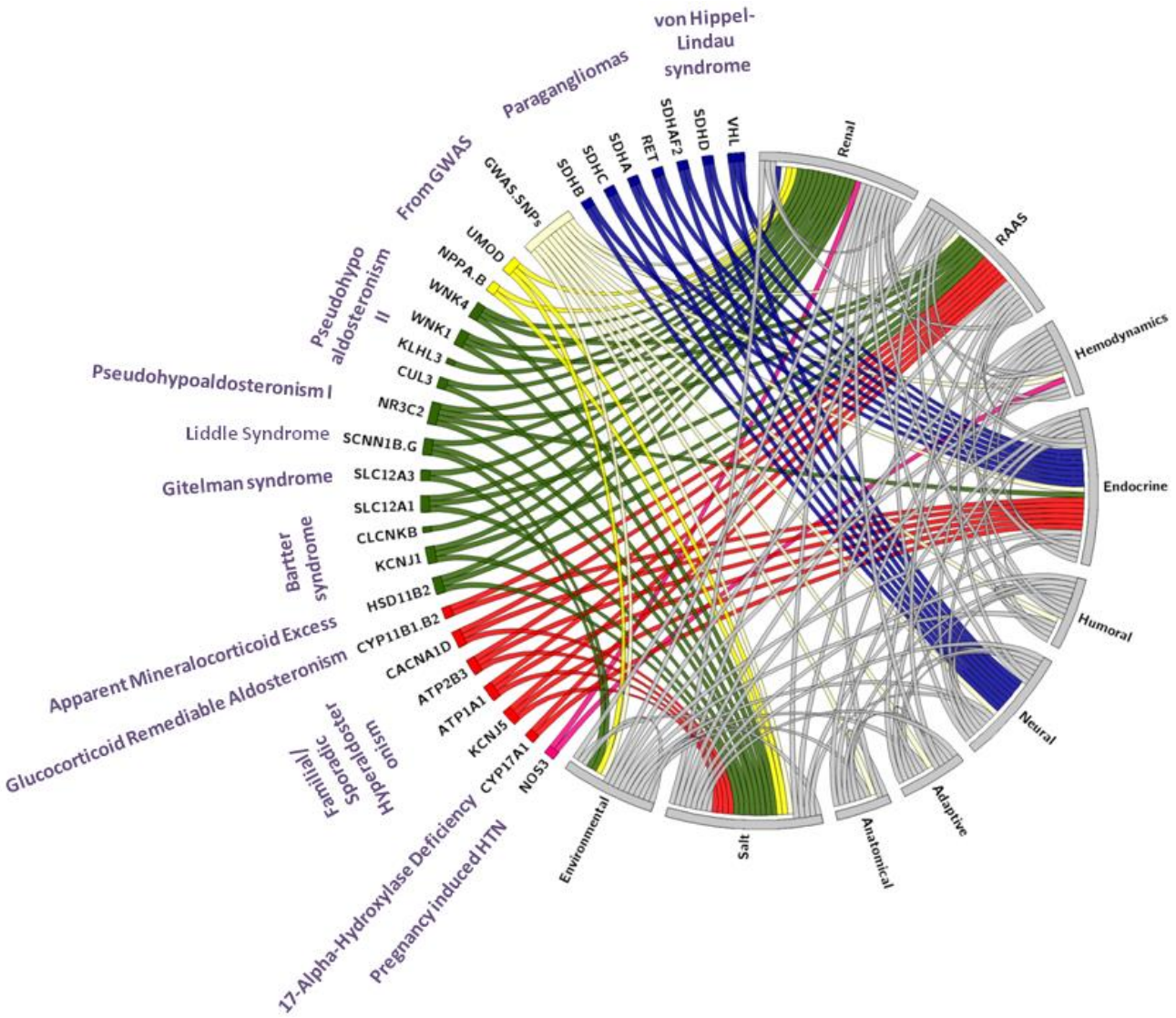
2015 – Updated Paige Model



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Monogenic Hypertension

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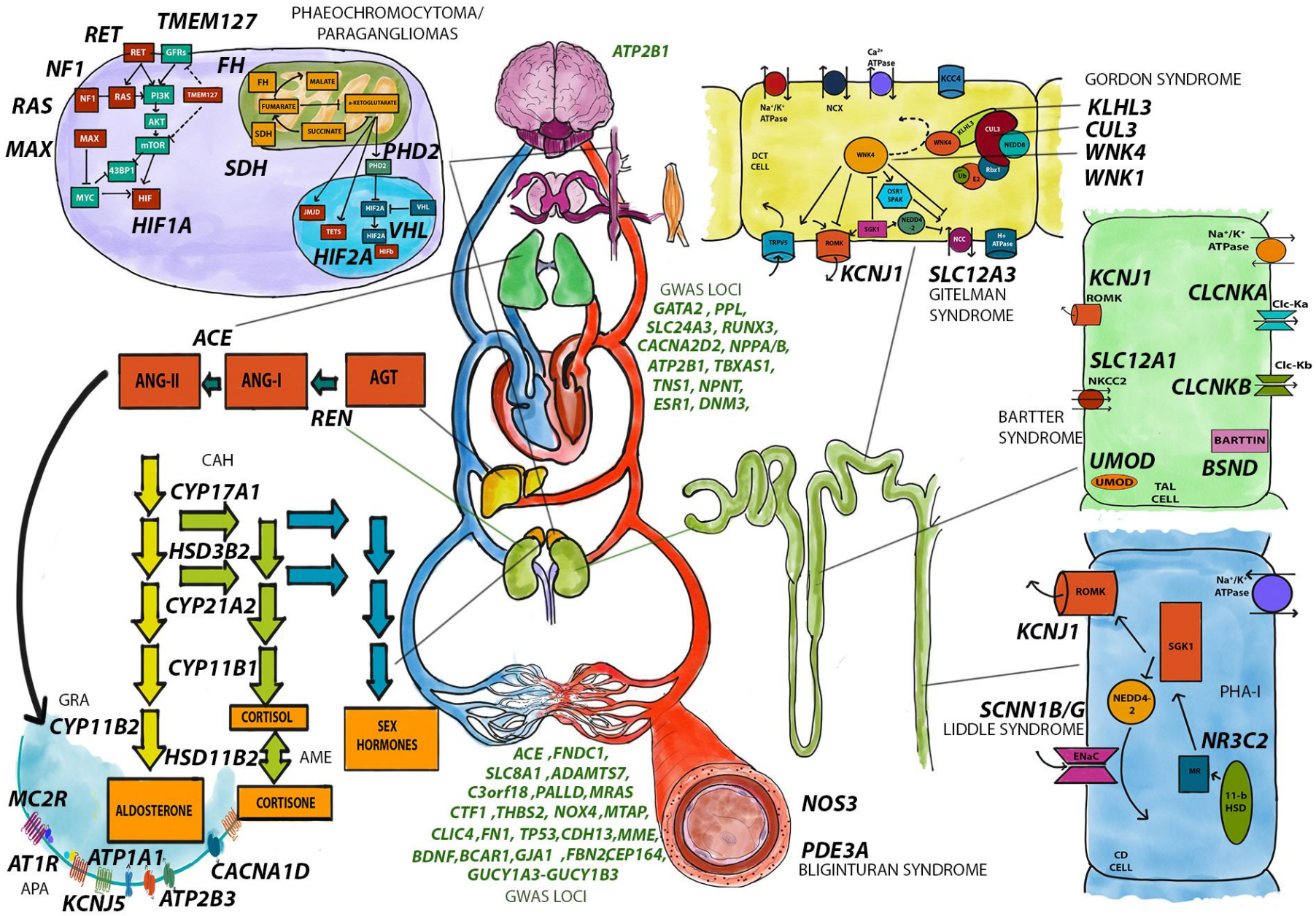
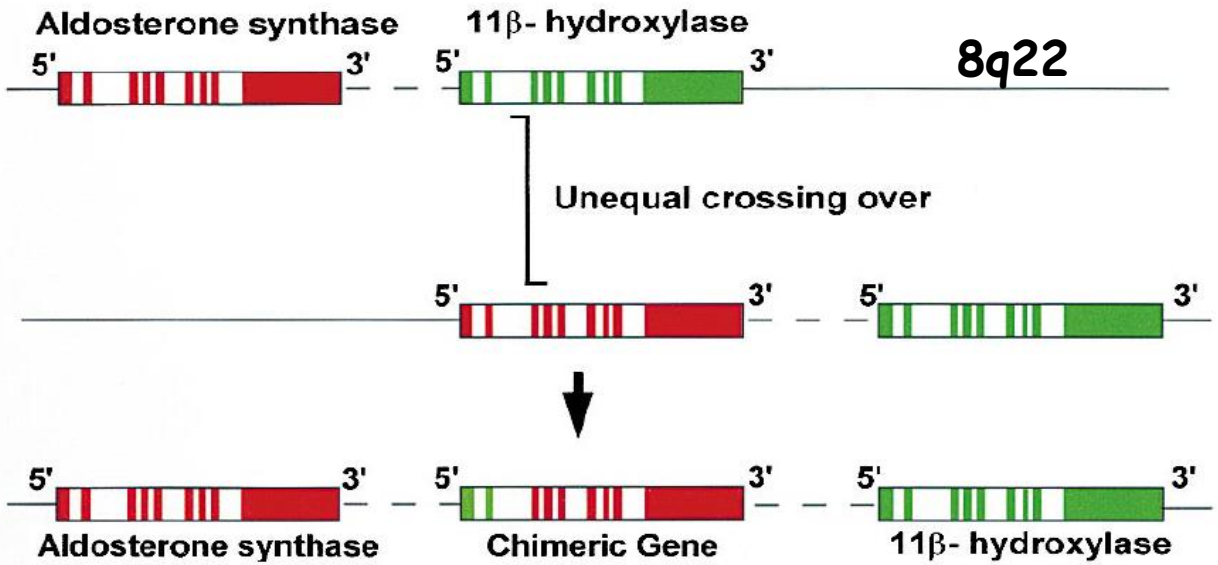
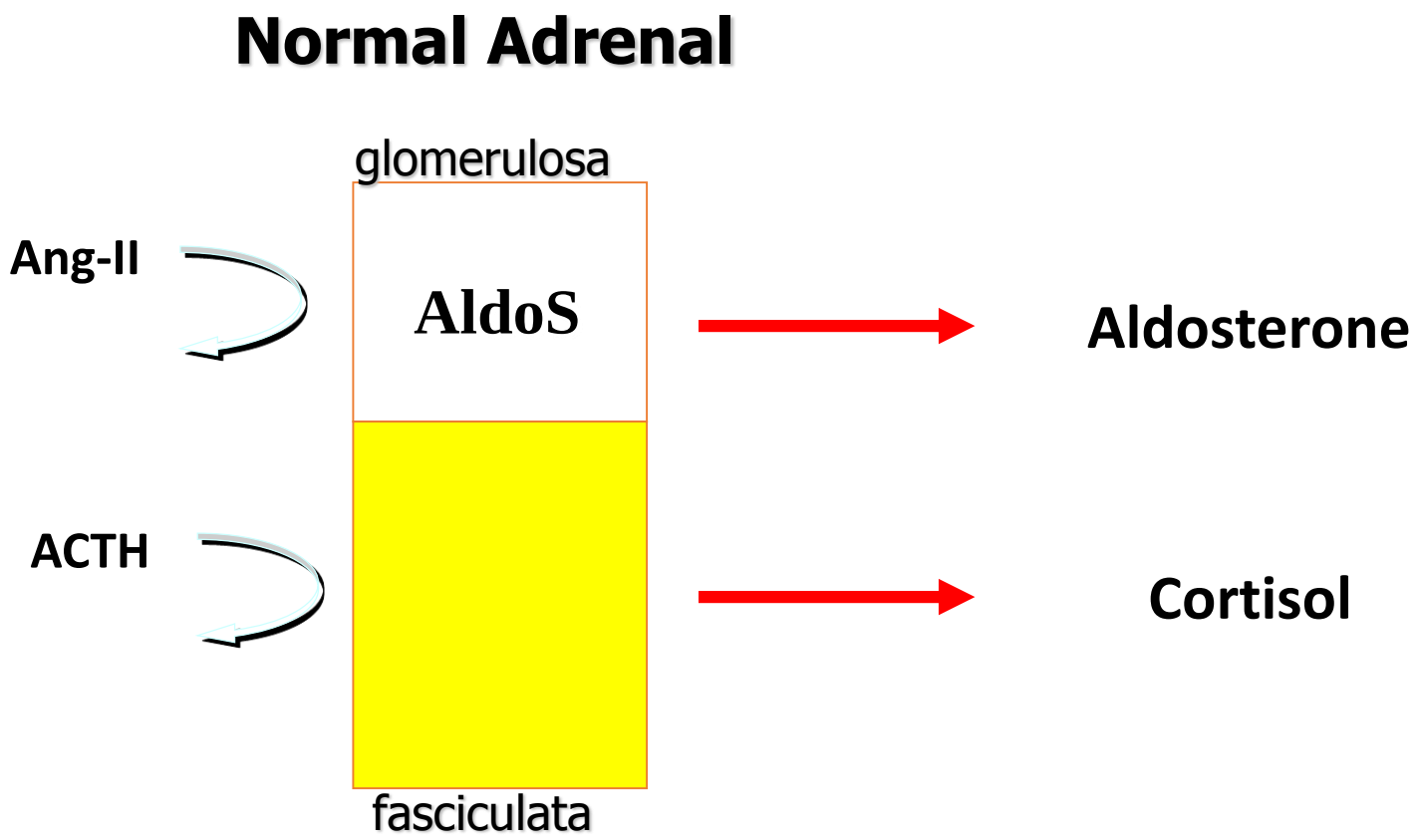


Padmanabhan and Joe, Physiological Reviews (submitted)

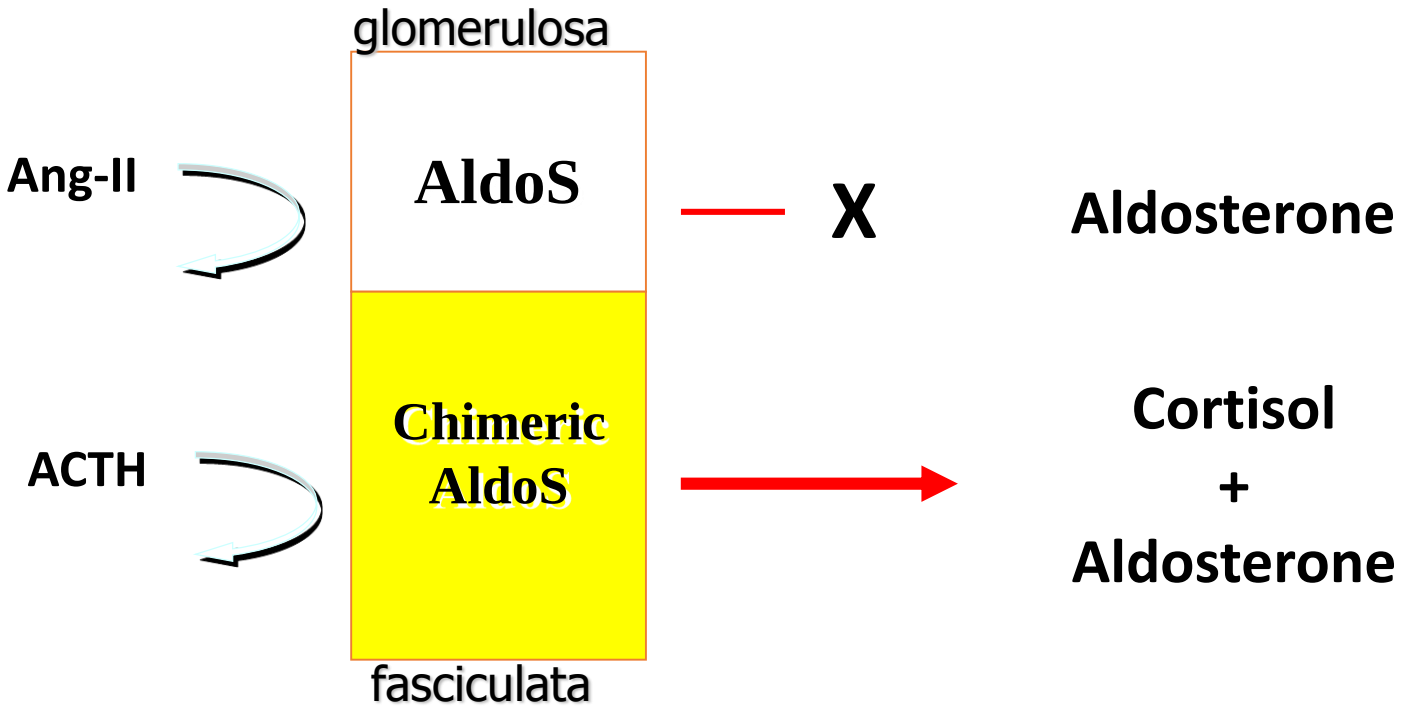
Glucocorticoid Remediable Aldosteronism



Glucocorticoid Remediable Hypertension

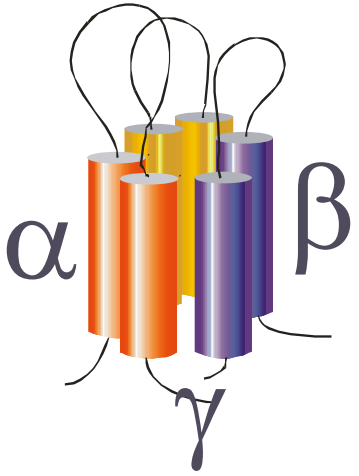


Glucocorticoid Remediable Hypertension



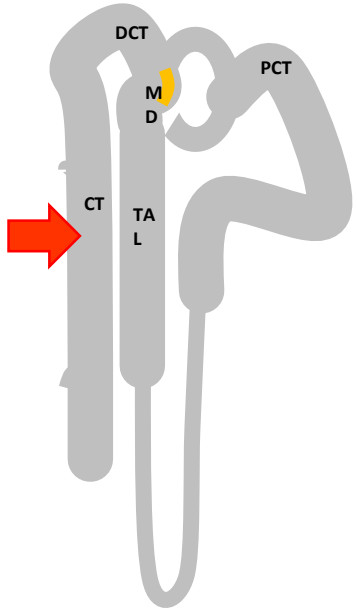
Treatment : low-dose glucocorticoids, amiloride, and spironolactone

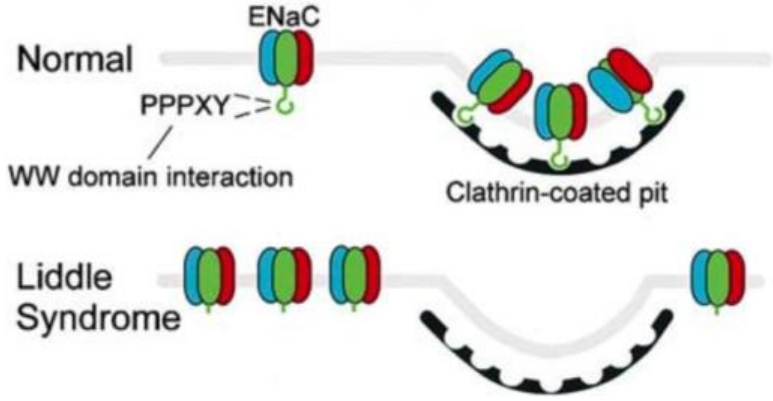
Liddle Syndrome



ENaC

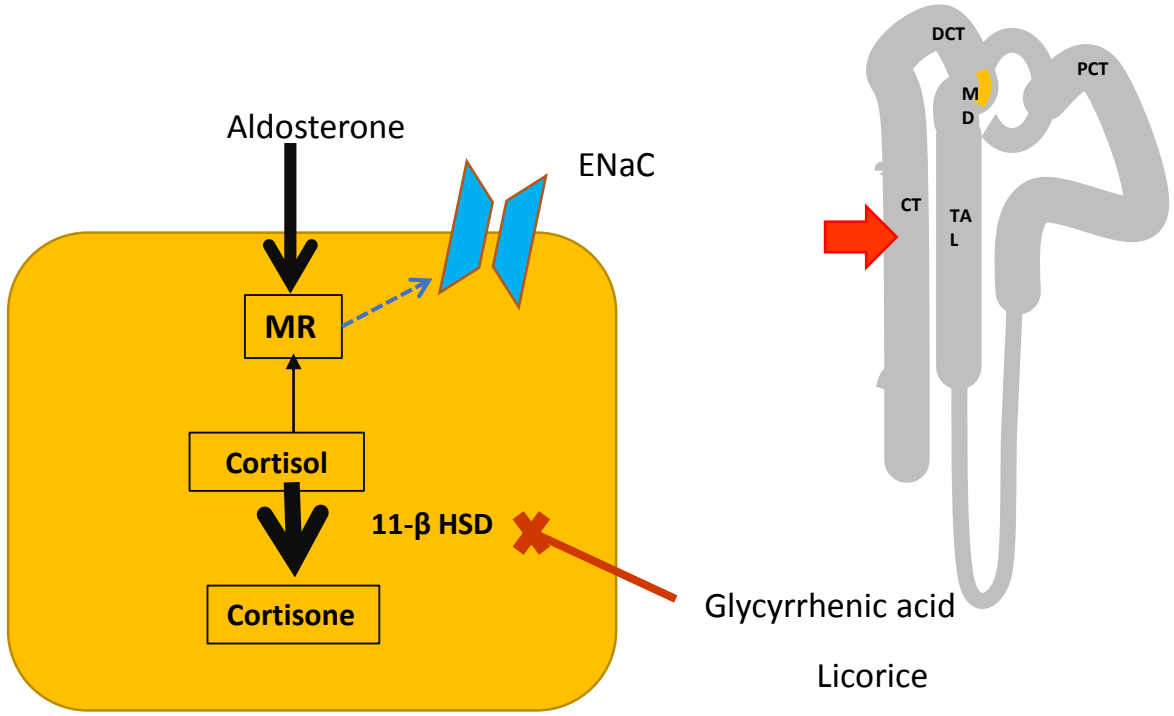
Nonsense mutations in C-terminus of b or g subunits cause constitutive activation of sodium channels





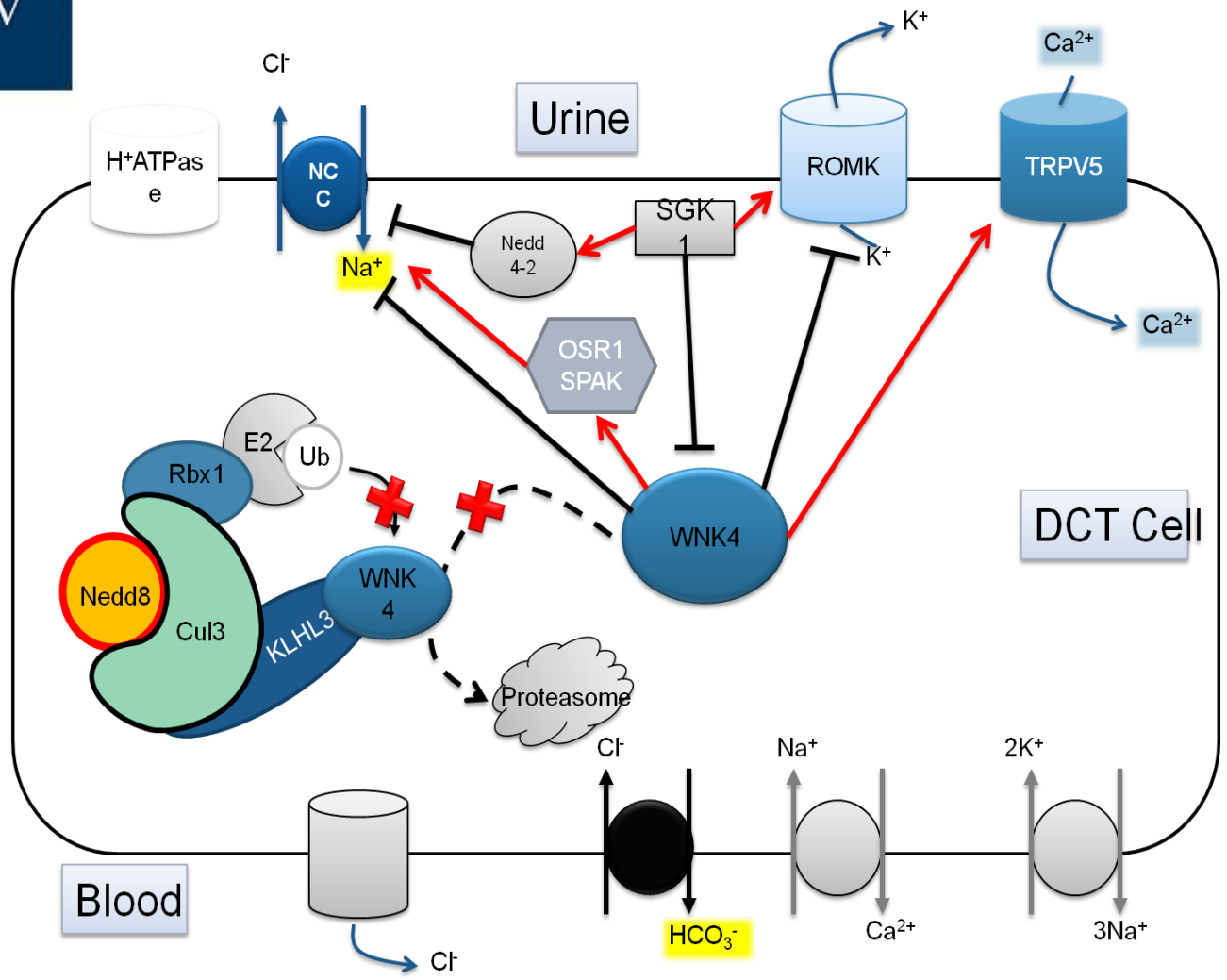
Treatment : Amiloride which blocks ENaC

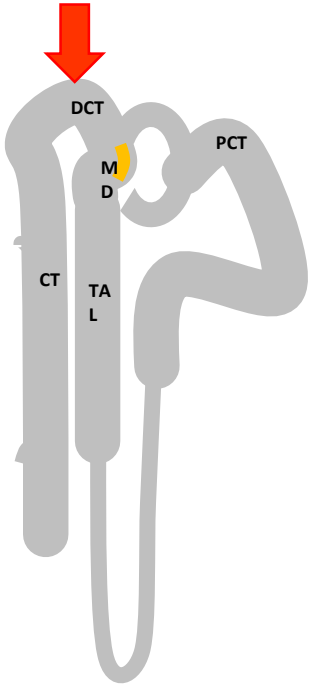
Apparent Mineralocorticoid Excess



Treatment: Low sodium diet and Spironolactone

Gordon's Syndrome



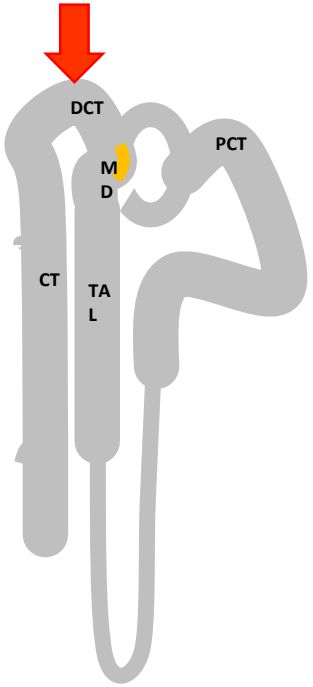


HTN associated with hyperkalemia, non-anion gap metabolic acidosis

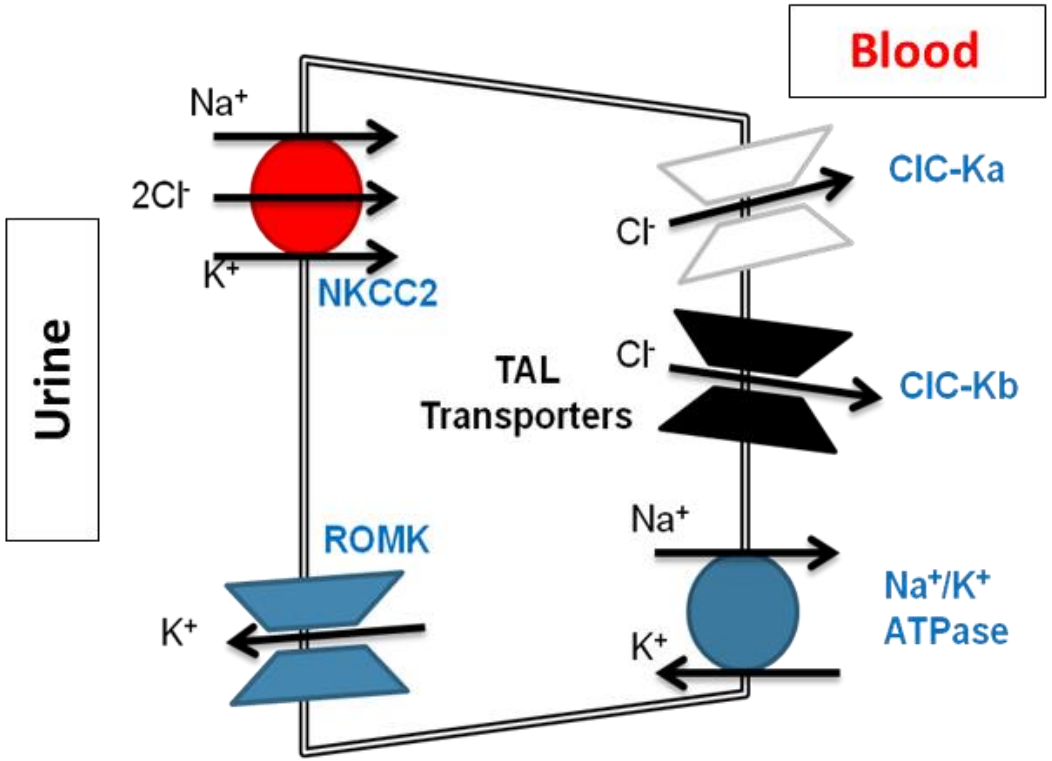
Treatment: Low-salt diet or thiazide diuretics

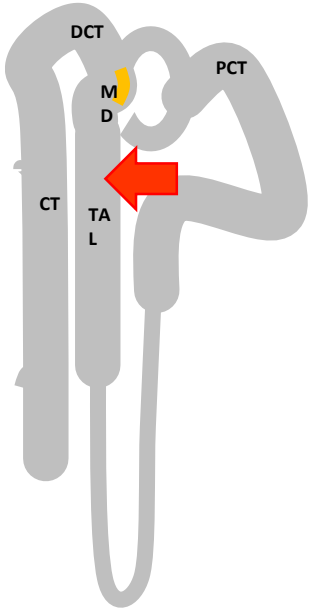
Gitelman's syndrome (Low BP)

- Loss of function mutations in Na-Cl cotransporter of the distal convoluted tubule
- Self-selected higher dietary salt intake in homozygous and heterozygous mutant individuals
- Much more common than Bartter syndrome
- Loss of function of NCCT (mutation in SCL12A3), hence resembles effect of thiazides
- Hypokalaemia, hypocalciuria and hypomagnesaemia, metabolic alkalosis
- Low blood pressure and secondary hyperreninaemic hyperaldosteronism
- Treatment with sodium, potassium and magnesium supplementation



Bartter Syndrome (Low BP)

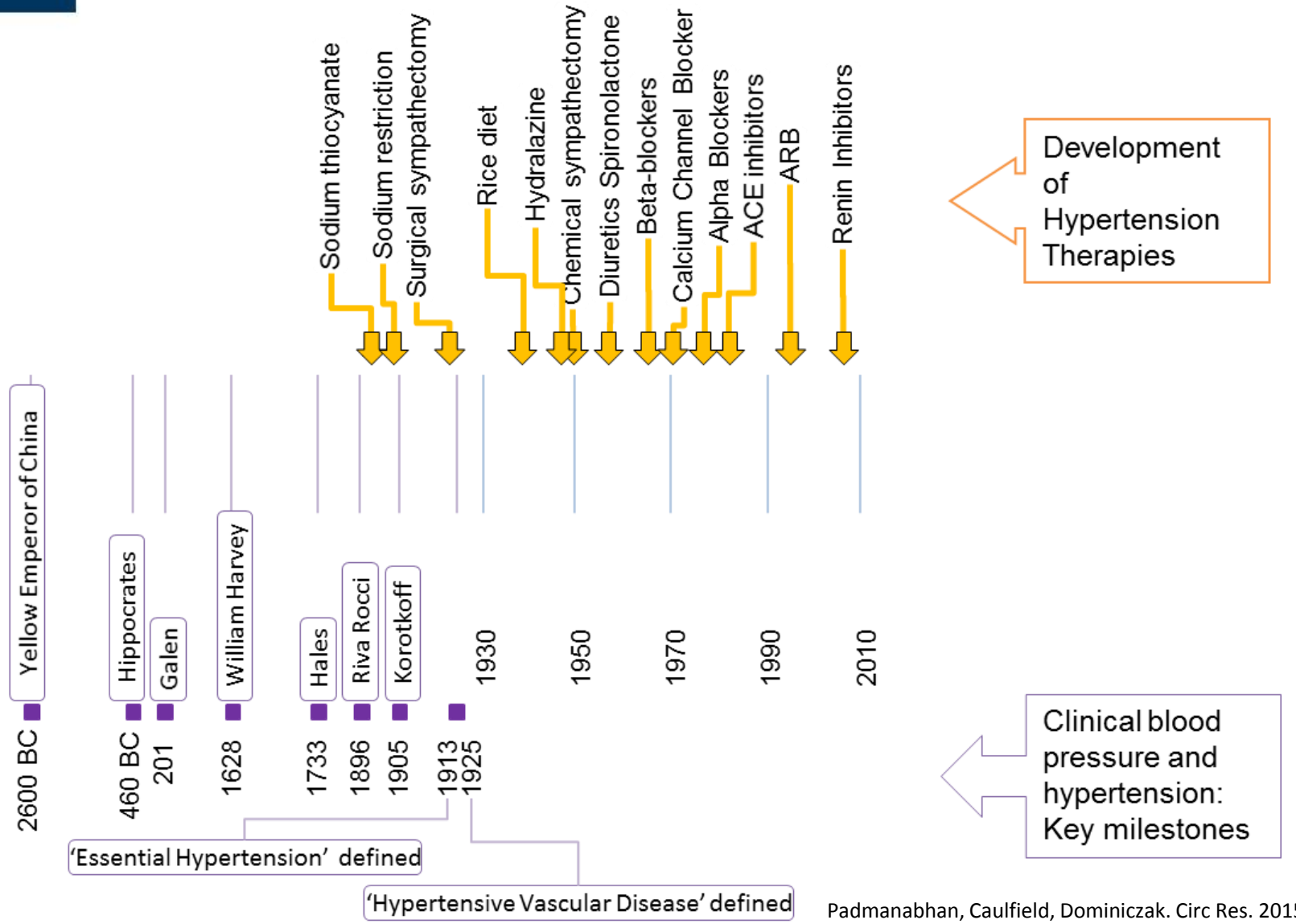




Dysfunction of NKCC2, hence resembles effect of treatment with loop diuretics

- Type 1 - defective NKCC2
- Type 2 - defective ROMK2, which regulates NKCC2 by recycling potassium back into tubule
- Type 3 - defective CLCKB, which permits NKCC2 by shuttling chloride out of LoH cells
- Type 4 - defective Barttin, a co-factor of CLCKB in kidney and ear, hence also causes deafness
- Severe salt-wasting presenting in early infancy - or with prematurity and polyhydramnios
- Treatment with sodium and potassium supplementation. •Indomethacin helpful in type 2

Hypertension - Treatment



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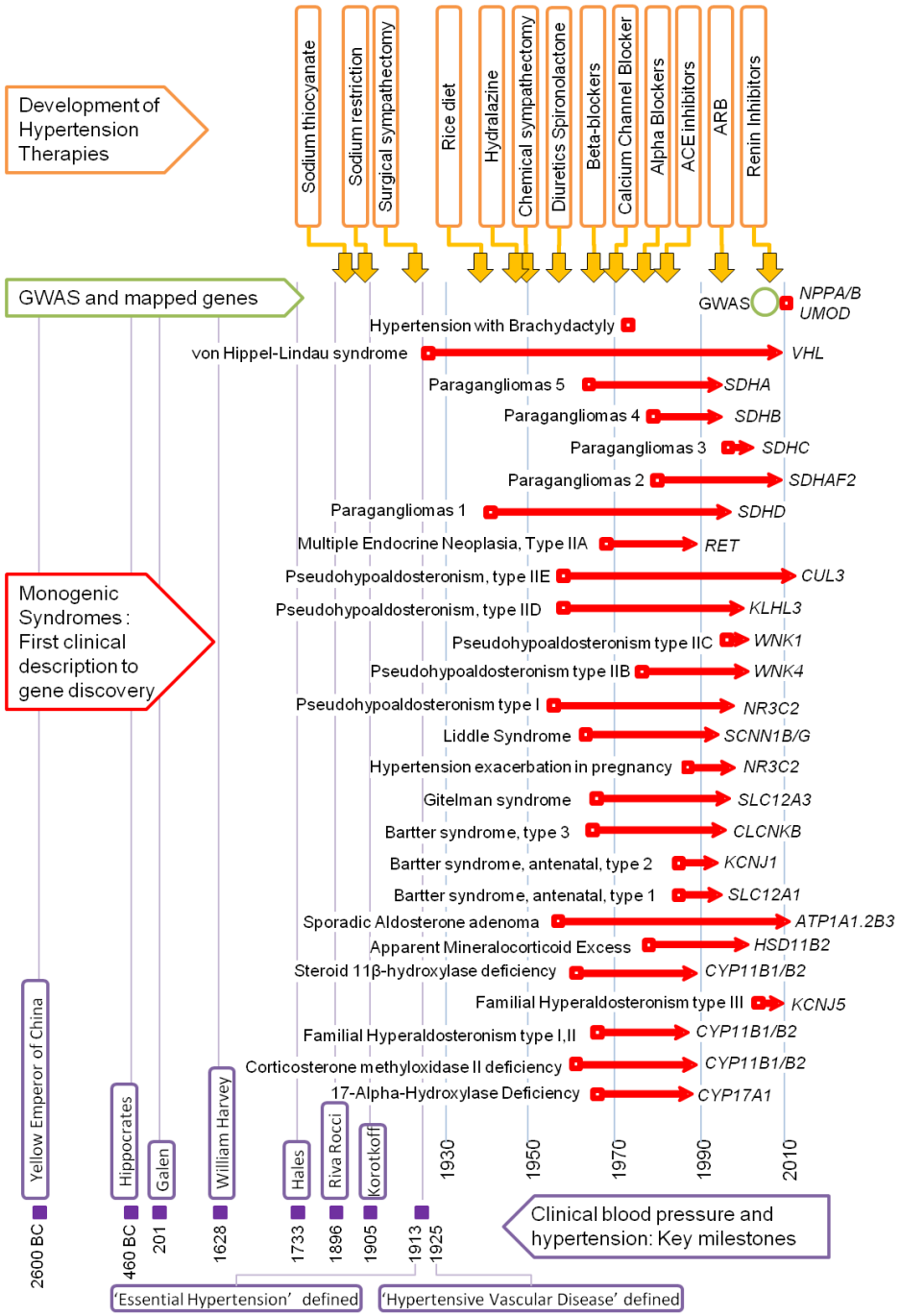

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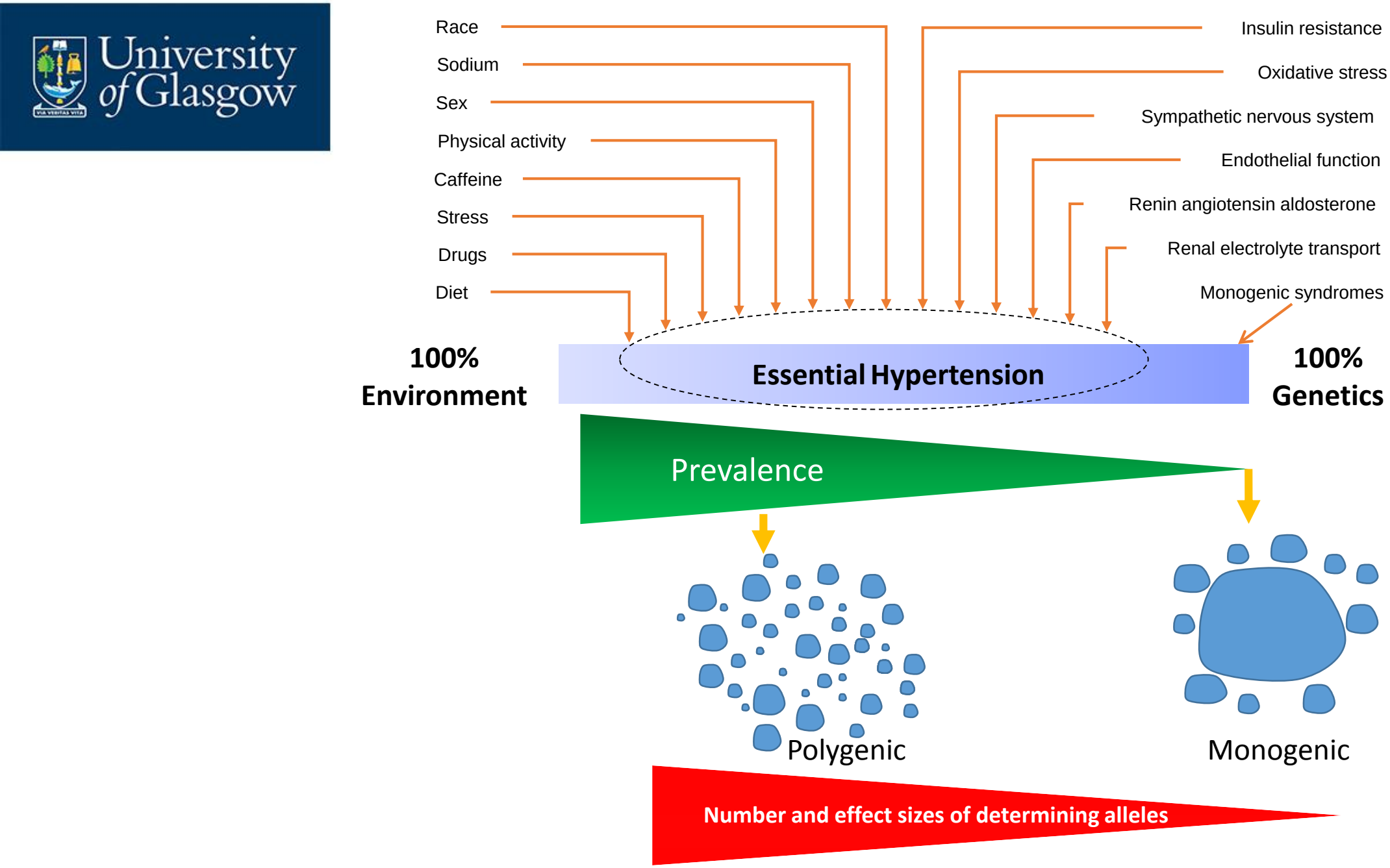
Polygenic Hypertension (Essential HTN)


Race
Sodium
Sex
Physical activity
Caffeine
Stress
Drugs
Diet
Insulin resistance
Oxidative stress
Sympathetic nervous system
Endothelial function
Renin angiotensin aldosterone
Renal electrolyte transport
Monogenic syndromes
100% Environment
Essential Hypertension
100% Genetics
Prevalence
Polygenic
Monogenic
Number and effect sizes of determining alleles

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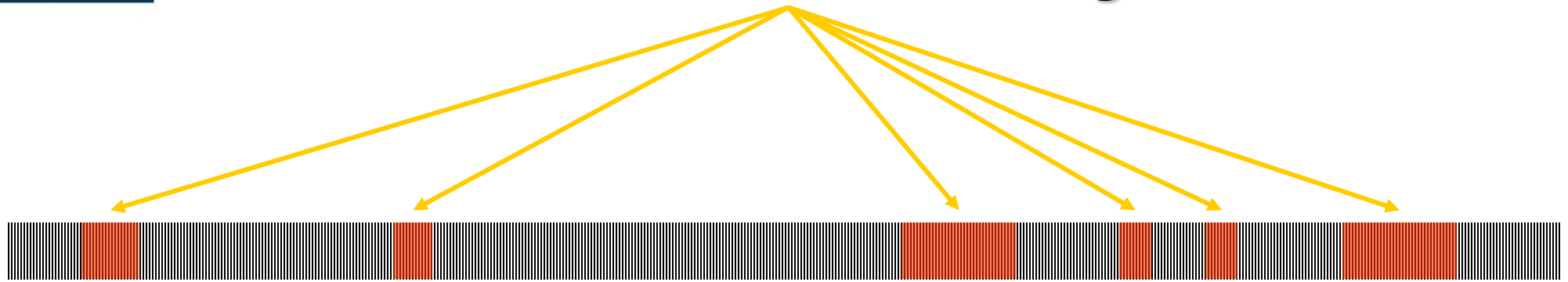
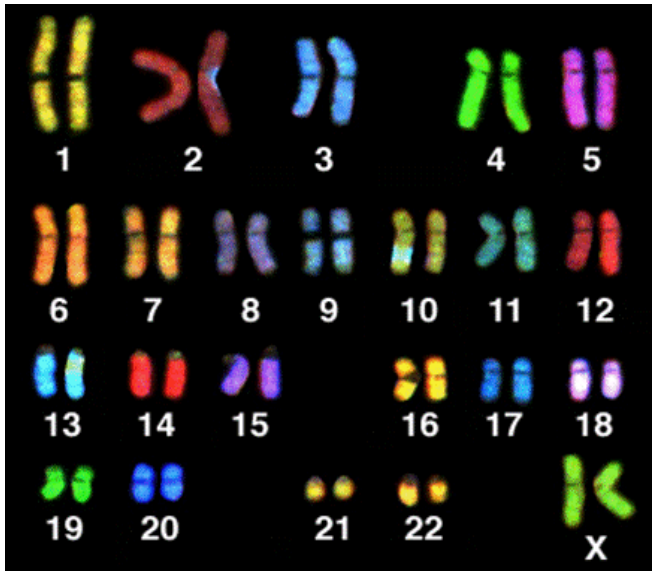
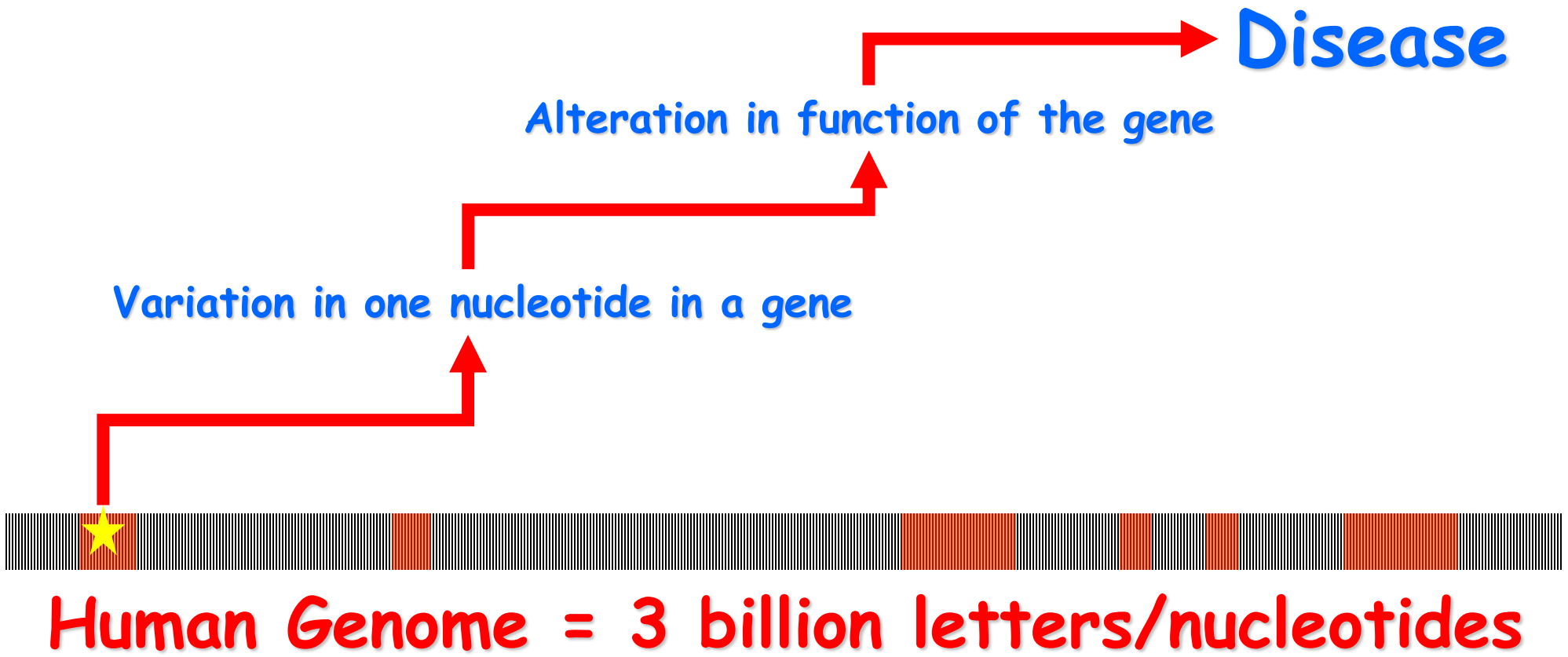
Human Genome = ~20,000 genes

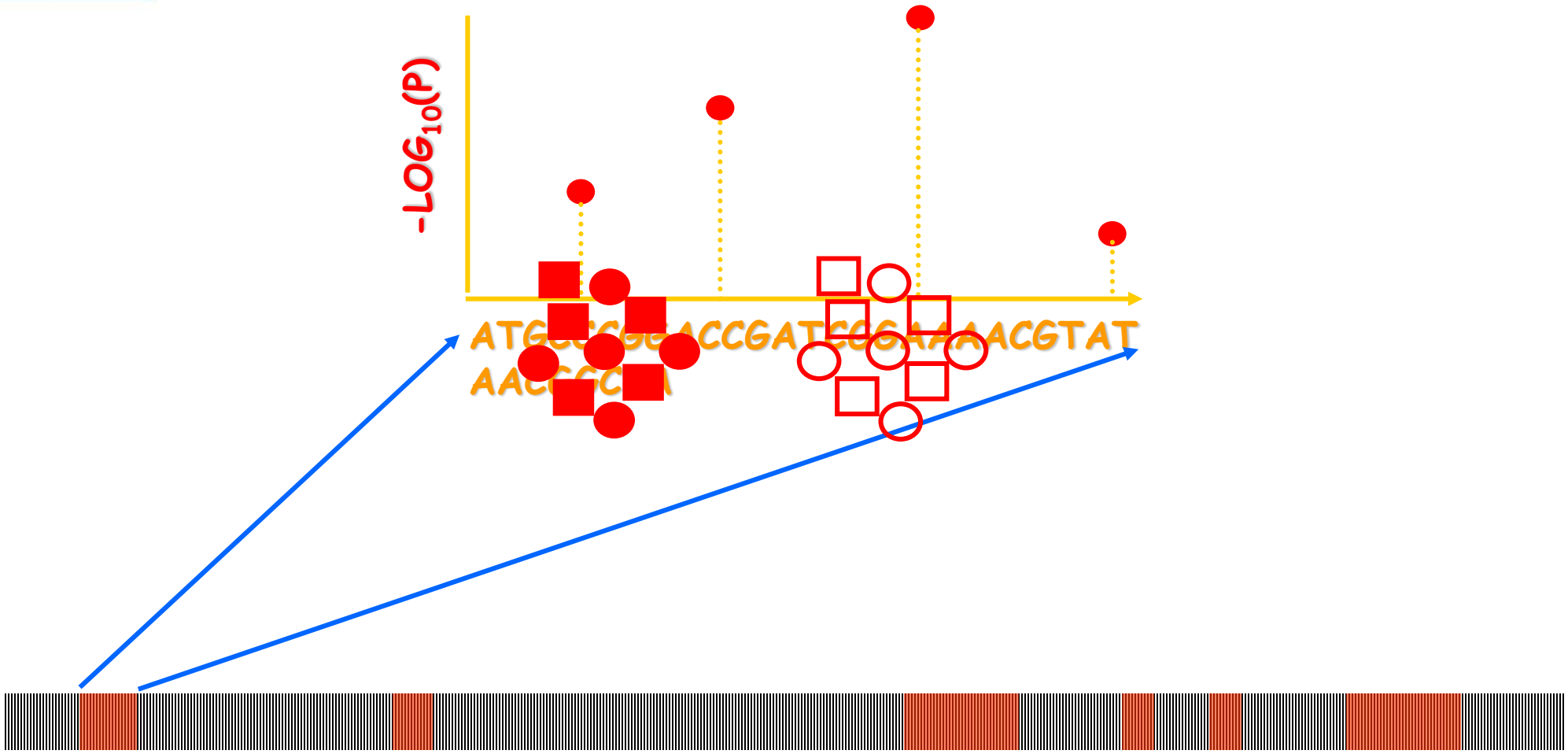


Human Genome = 3 billion letters/nucleotides




Disease
Alteration in function of the gene
Variation in one nucleotide in a gene
Human Genome = 3 billion letters/nucleotides

Candidate Gene Study



Human Genome = 3 billion letters/nucleotides

The candidate gene approach

The genome wide approach

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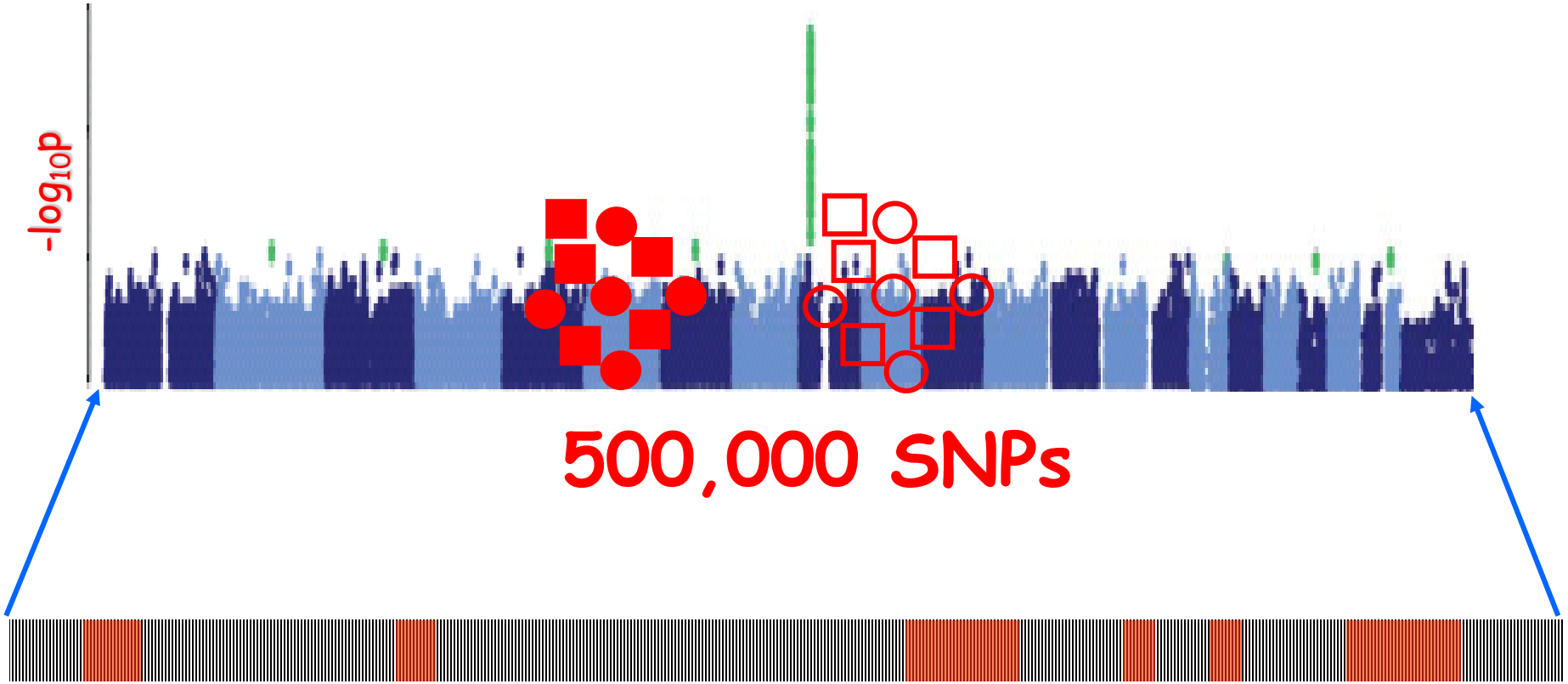
Genome Wide Association



Human Genome = 3 billion nucleotides

AIM-HY INFORM

Ancestry Informative Markers in Hypertension (AIM HY) Programme

ComparIsoN oF Optimal Hypertension RegiMens (Part of the Ancestry Informative Markers in Hypertension (AIM HY) Programme – AIM HY-INFORM)

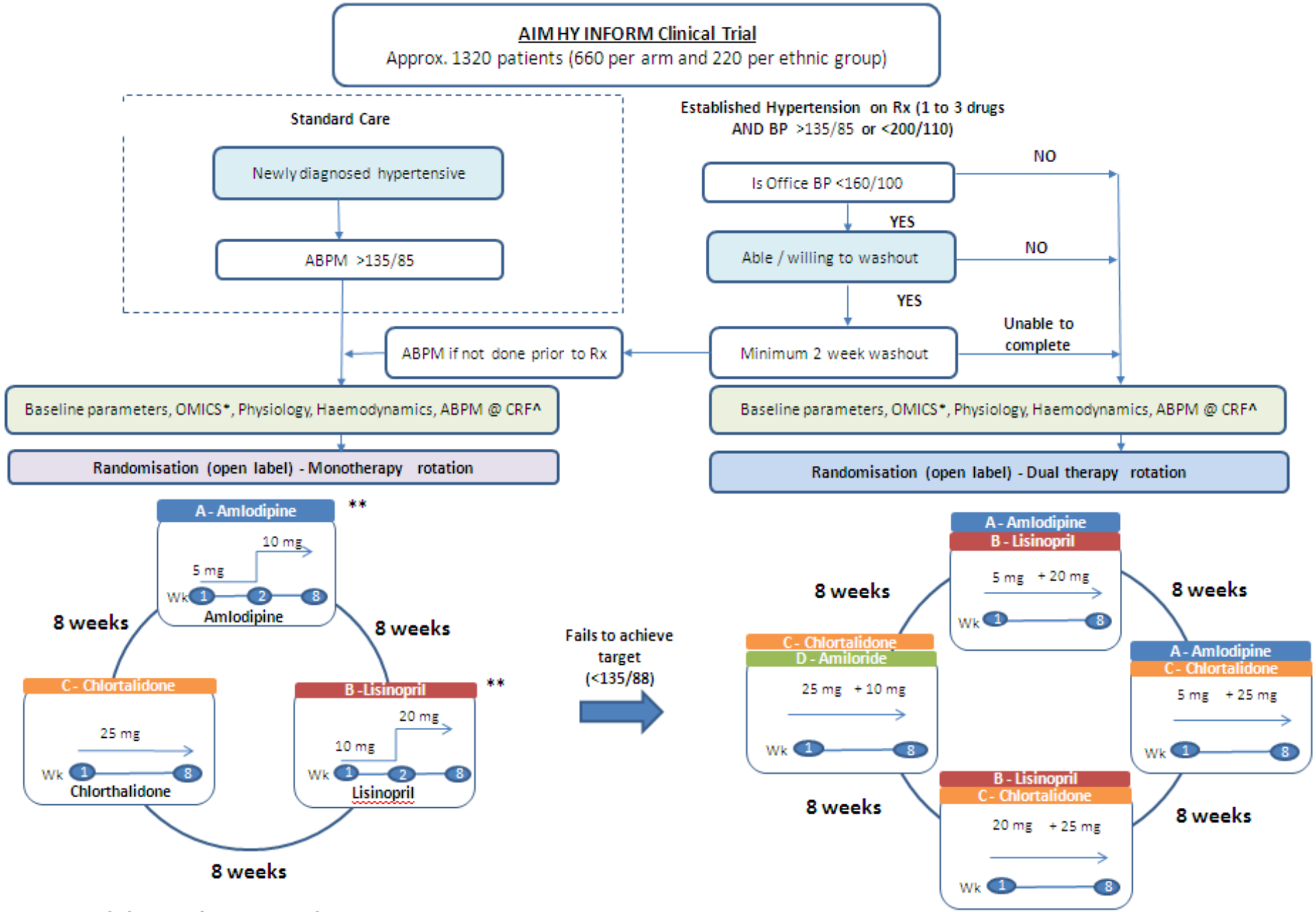
Background and Aims

NICE guidance (CG127) stratifies hypertension treatment according to age and self-defined ethnicity (SDE).

The evidence-base supporting the current guidance on SDE stratification is limited, and there is a specific lack of data from UK-based populations.

Aim

To provide an optimal choice of anti-hypertensive therapy from existing first-line-drugs (and differing combinations thereof) in a multi-ethnic population in the UK.



•:OMICS = *Metabolomic and Genomic analysis*

**: *Dose up-titration in 1 or 2 weeks depending on patient response*

^ : *CRF = Clinical Research Facility*

Outcome of AIM-HY INFORM

This trial will provide the first prospective evidence for best treatment choice according to SDE for White, Black and Asian populations in the UK.

This should reduce the number of consultations; time required to achieve optimal blood pressure control and the contribution to better hypertension control in the UK.

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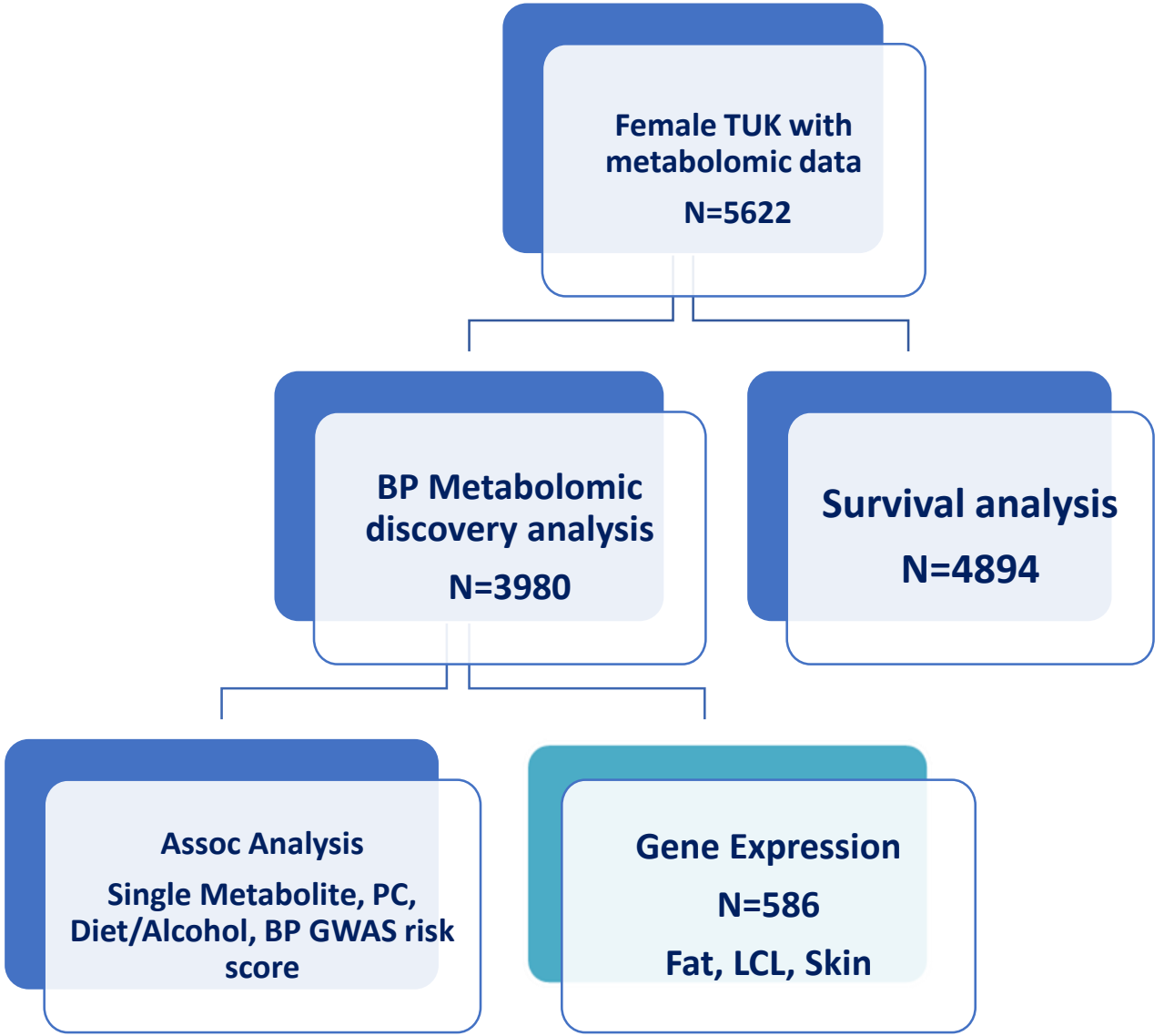
Metabolomics

ANALYSIS PIPELINE in TwinsUK



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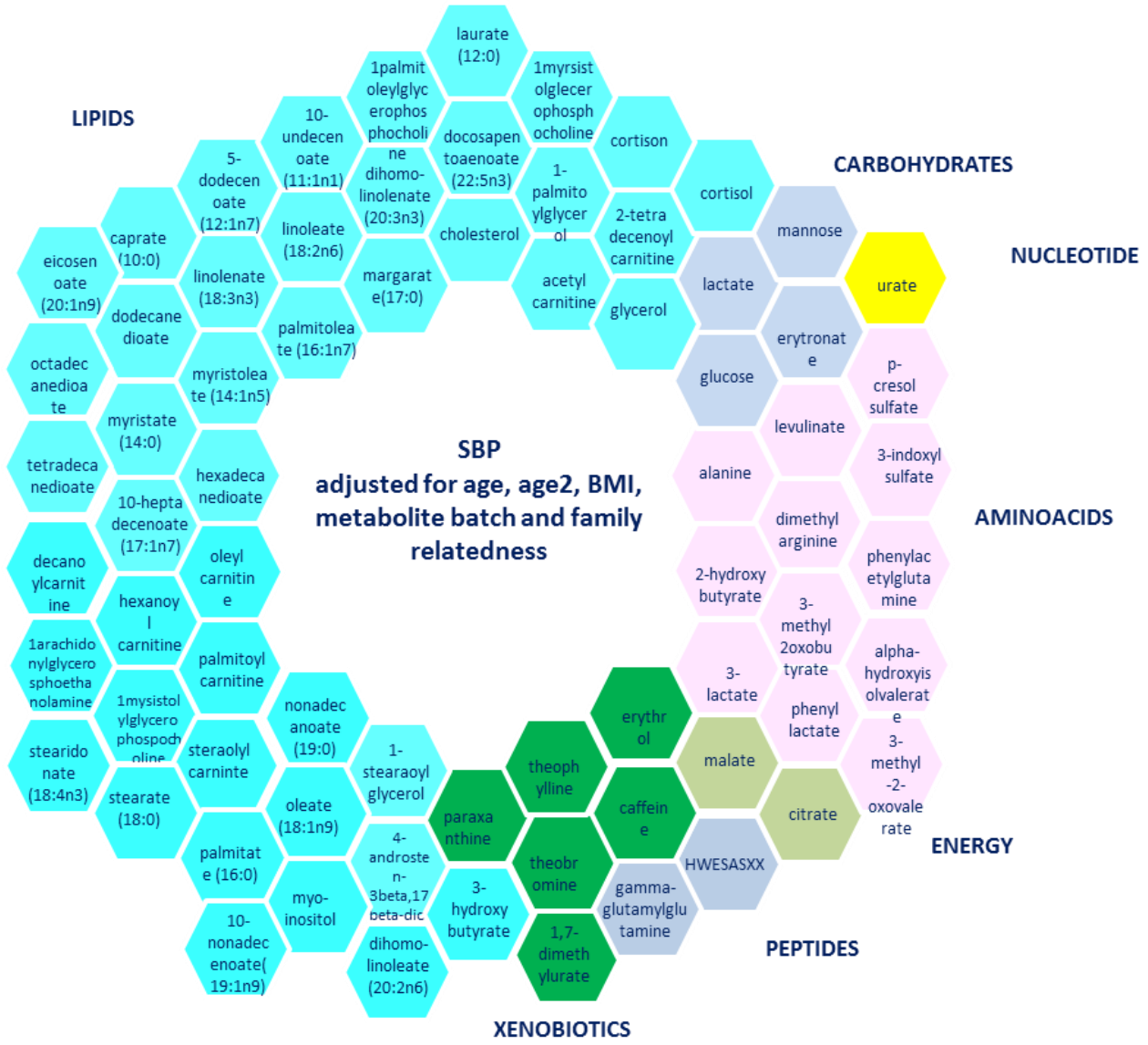
Metabolomics of SBP



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Refining the Signal

Metabolite	SBP		DBP	
	Beta [95% CI]	P	Beta [95% CI]	P
phenylacetylglutamine	-1.04[-1.53;-0.55]	$3.64x10^{-5}$	-0.66[-0.97;-0.34]	$5.62x10^{-5}$
lactate	1.51[0.99;2.02]	$1.24x10^{-8}$	0.94[0.61;1.27]	$2.54x10^{-8}$
octanoylcarnitine	1.37[0.91;1.83]	$4.98x10^{-9}$	0.78[0.48;1.08]	$5.30x10^{-7}$
stearoylcarnitine	0.98[0.52;1.44]	$3.29x10^{-5}$	0.67[0.36;0.97]	$1.66x10^{-5}$
hexadecanedioate	**1.31[0.83;1.78]**	**$6.81x10^{-8}$**	**0.81[0.5;1.11]**	**$2.96x10^{-7}$**
tetradecanedioate	1.57[1.07;2.07]	$8.45x10^{-10}$	0.88[0.56;1.21]	$1.18x10^{-7}$
10-heptadecenoate (17:1n7)	1.3[0.83;1.77]	$6.45x10^{-8}$	0.9[0.59;1.22]	$2.40x10^{-8}$
dihomo-linoleate (20:2n6)	**1.94[1.5;2.38]**	**$1.40x10^{-17}$**	**1.13[0.82;1.44]**	**$5.55x10^{-13}$**
nonadecanoate (19:0)	0.91[0.47;1.36]	$6.86x10^{-5}$	0.61[0.31;0.92]	$9.08x10^{-5}$
palmitate (16:0)	1.85[1.4;2.3]	$7.76x10^{-16}$	1.09[0.78;1.4]	$1.03x10^{-11}$
5-dodecenoate (12:1n7)	1.76[1.3;2.23]	$1.97x10^{-13}$	0.94[0.63;1.25]	$2.75x10^{-9}$
4-androsten-3beta,17beta-diol disulfate 1*	1.82[1.25;2.38]	$3.95x10^{-10}$	1.25[0.87;1.63]	$1.40x10^{-10}$
cortisol	1.66[1.21;2.11]	$6.68x10^{-13}$	0.89[0.58;1.2]	$1.63x10^{-8}$
HWESASXX*	0.94[0.48;1.4]	$5.87x10^{-5}$	0.72[0.42;1.03]	$3.64x10^{-6}$
caffeine	**1.46[1;1.92]**	**$6.88x10^{-10}$**	**0.96[0.65;1.27]**	**$1.08x10^{-9}$**

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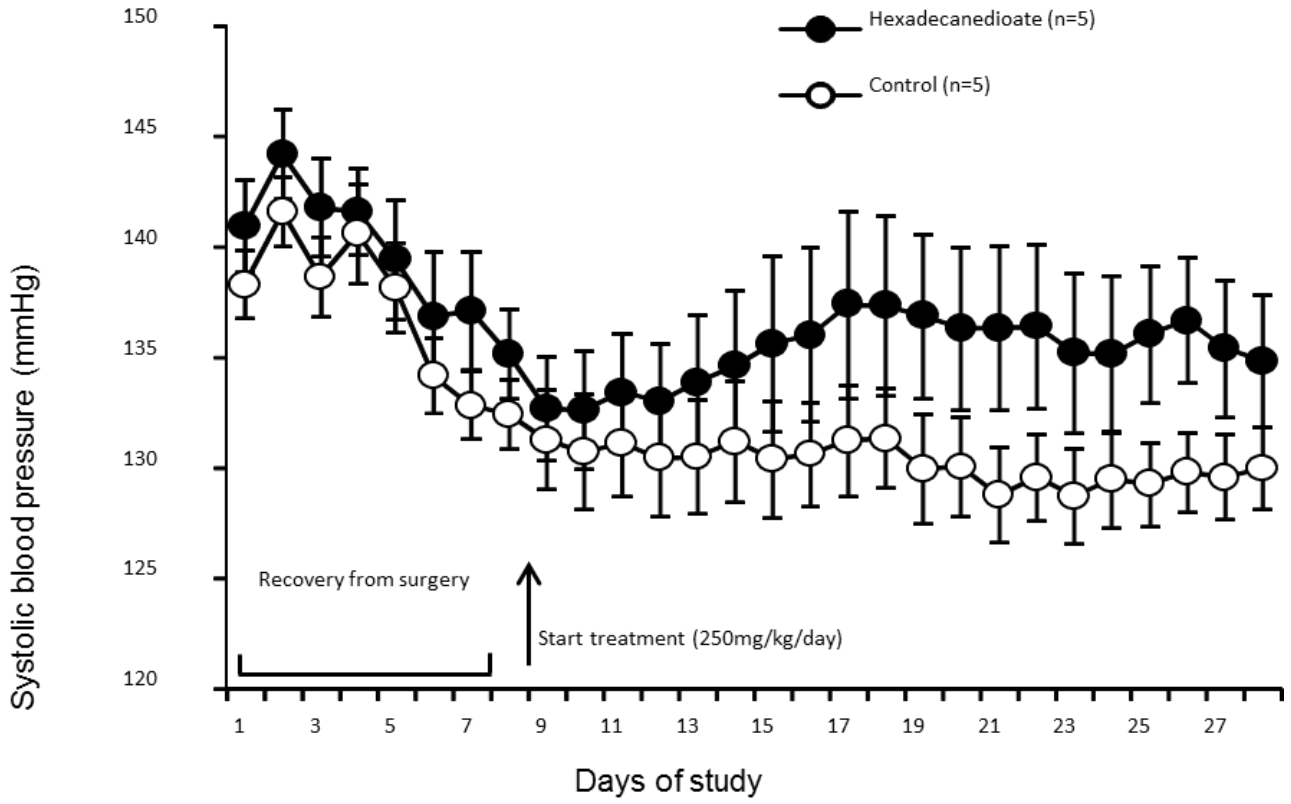
BP after oral hexadecanedioate



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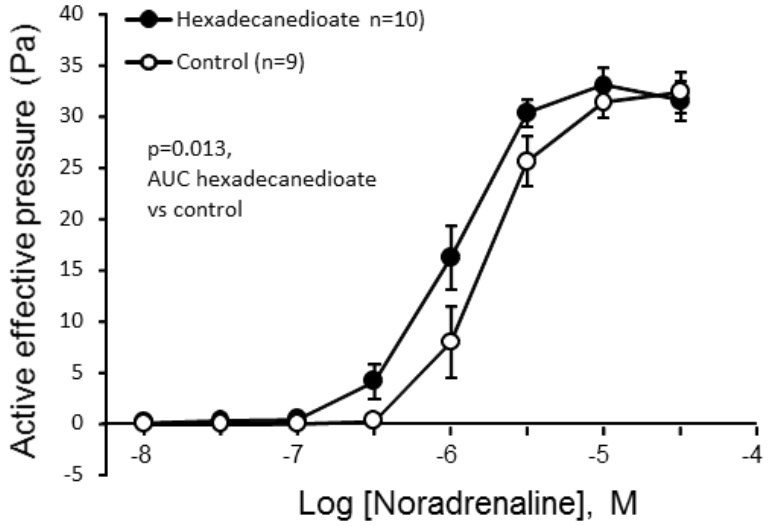
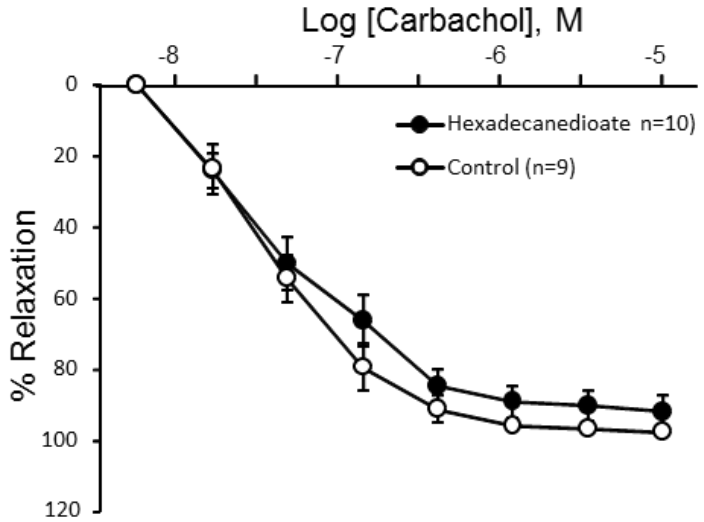
Mesenteric Artery Studies





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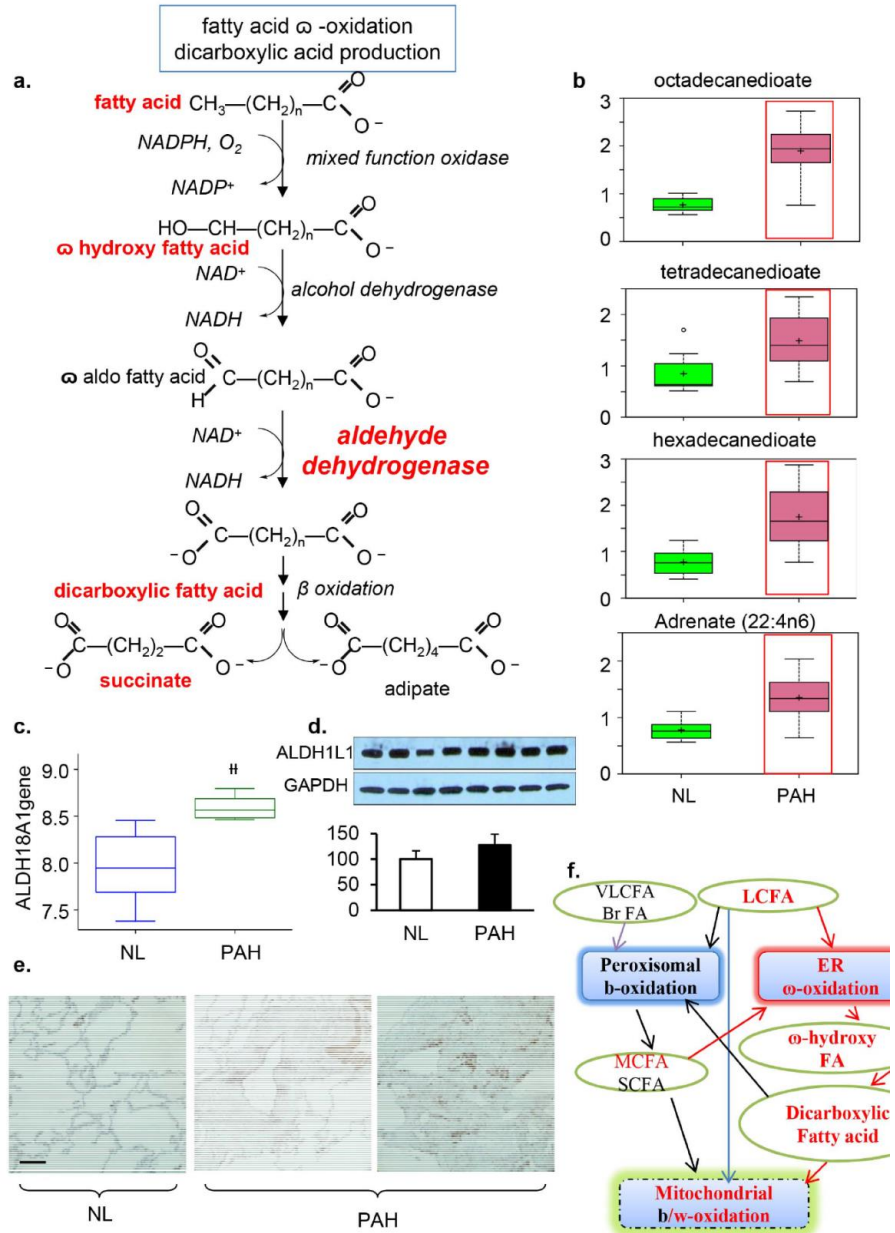
PLOS ONE

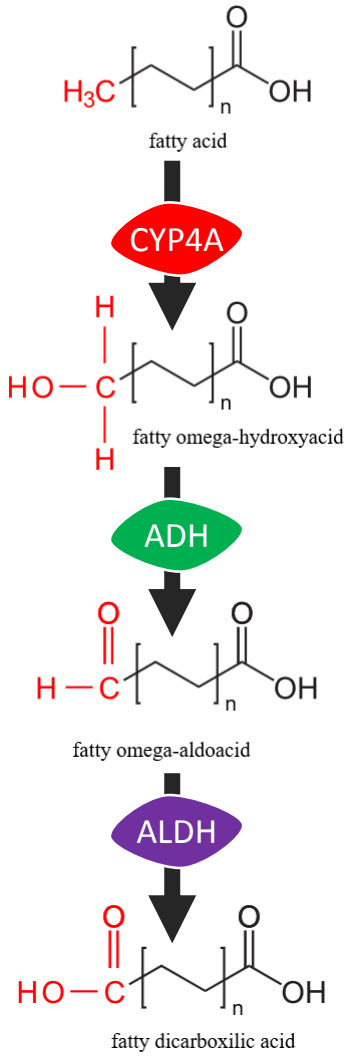
Metabolomic Heterogeneity of Pulmonary Arterial Hypertension

Yidan Zhao*, Jenny Peng, Catherine Lu, Michael Hsin, Marco Mura, Licun Wu, Lei Chu, Ricardo Zamel, Tiago Machuca, Thomas Waddell, Mingyao Liu, Shaf Keshavjee, John Granton, Marc de Perrot*

Latner Thoracic Surgery Research Laboratories and Division of Thoracic Surgery, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada



Fatty Acid ω oxidation pathway



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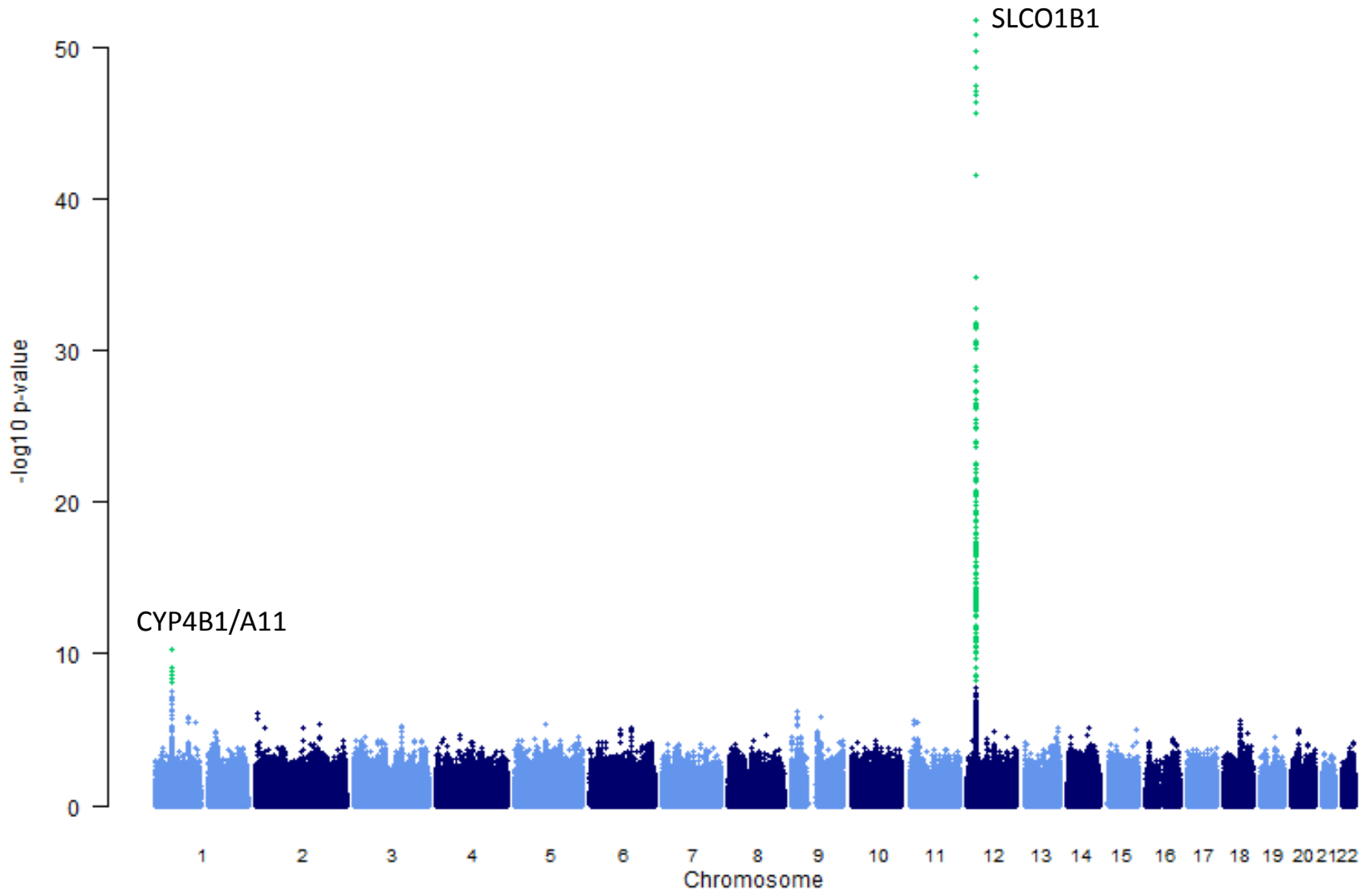
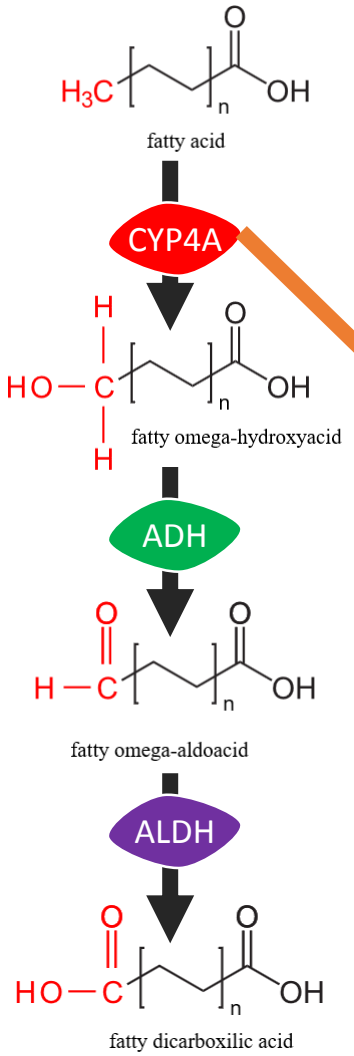
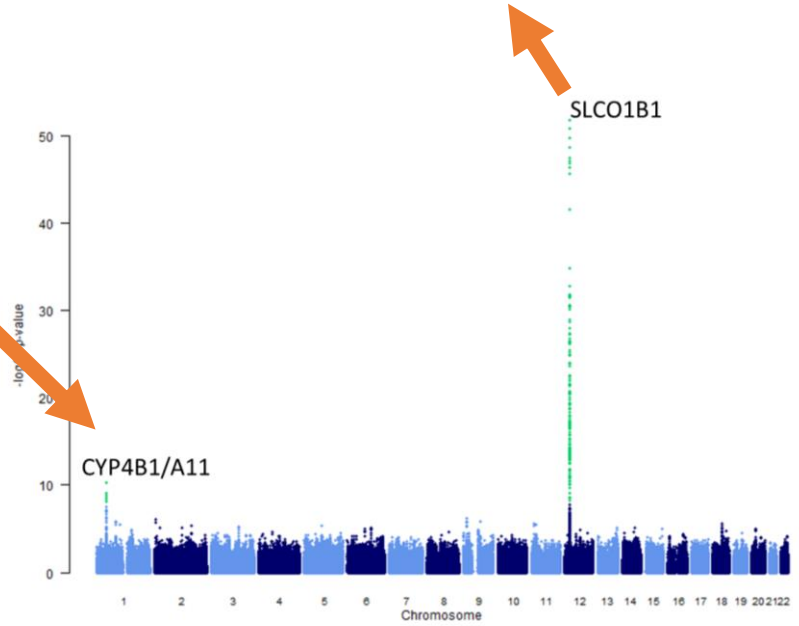
GWAS of Hexadecanedioate



Fatty Acid ω oxidation pathway



- Not known to be associated with fatty acid omega oxidation
- Associated with Statin myopathy

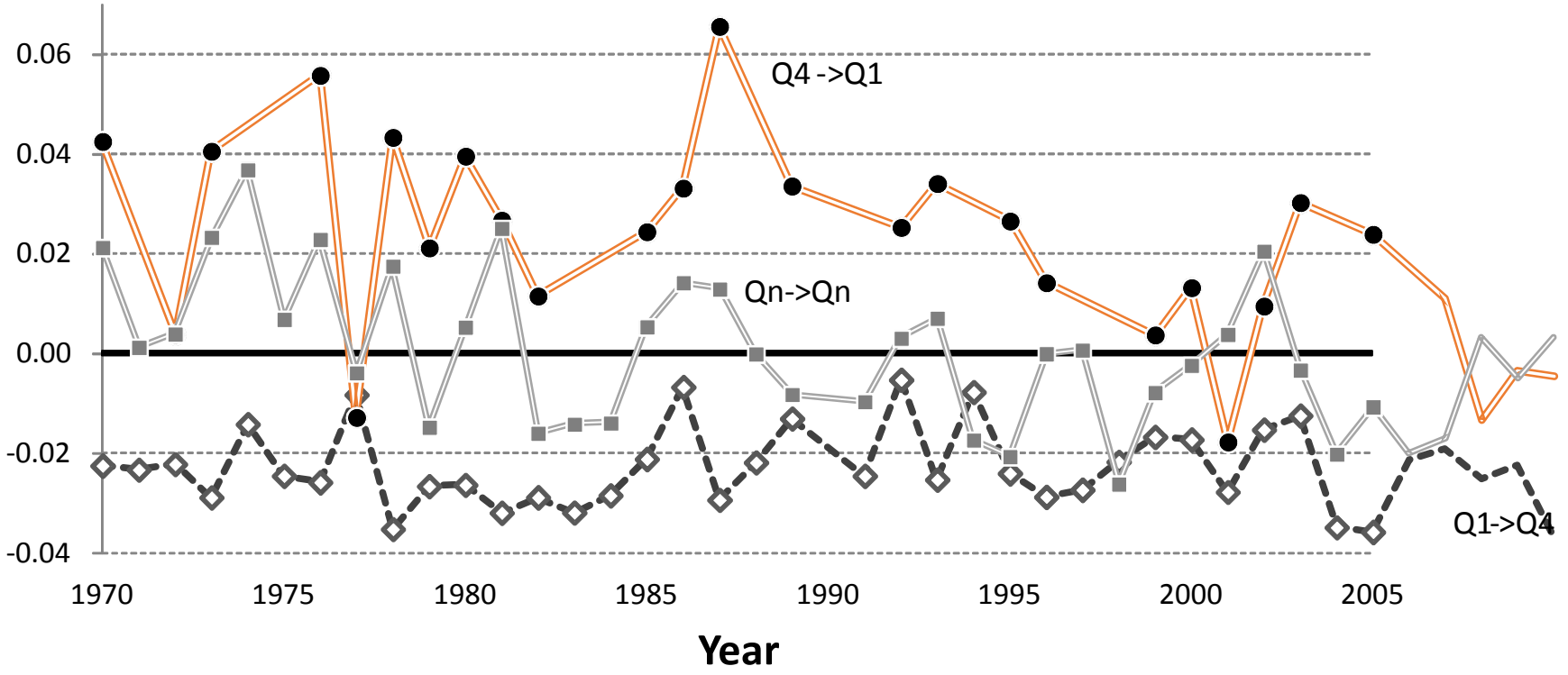


Big(ish) Data

Glasgow BP Clinic

- 17,011 patients attendees since 1968
- All clinical data including anthropometry, blood pressure, medications recorded at each visit – 180,000 visits
- All biochemistry and haematology tests recorded – at least annually – 2.3 million
- Record linkage for mortality ICD-10
- Record linkage for hospital admissions – 173,386 from 1980
- Refill prescriptions – 5 million since 2004
- Geocoding - location, area level deprivation, social and environmental variables – pollution, green space, distance to doctor/supermarket, weather

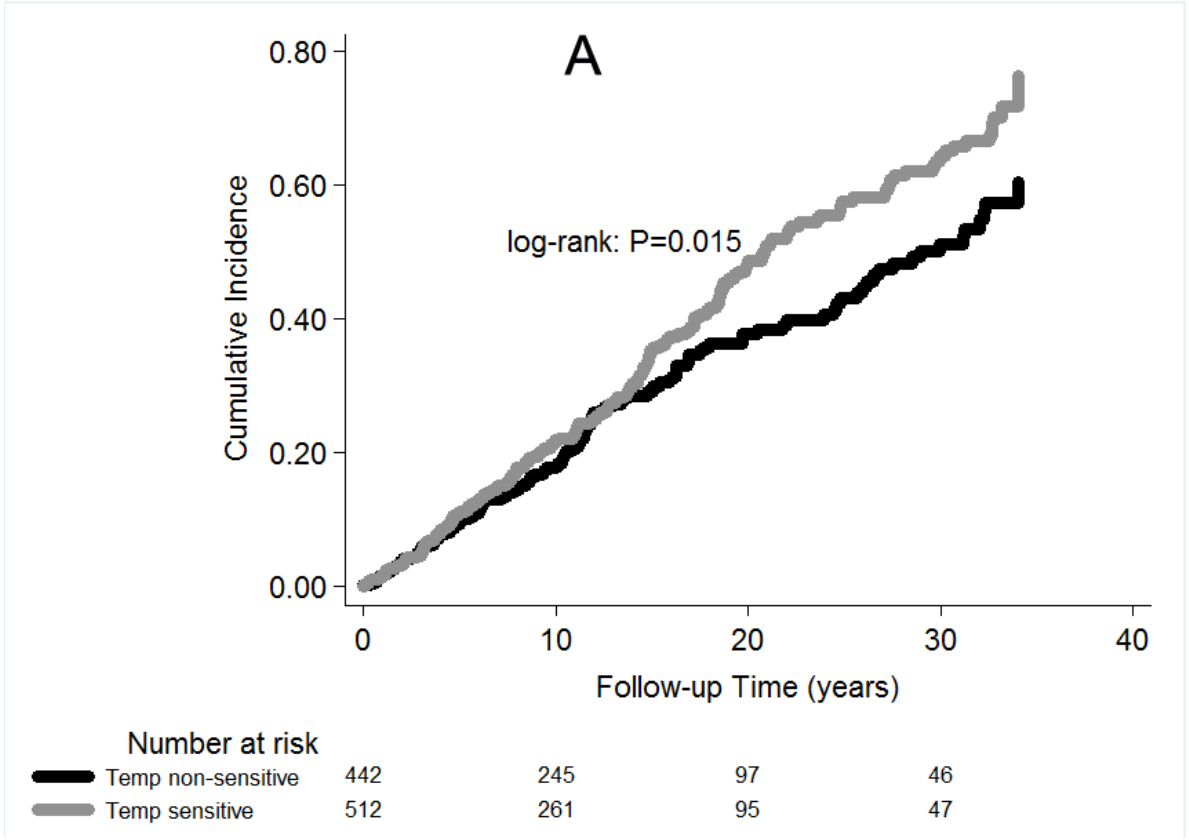
Patterns of systolic blood pressure (SBP) change annually across sequential visits.



>169 000 clinic visits of 16 010 Glasgow Blood Pressure Clinic patients with hypertension
Each clinic visit mapped to the mean West of Scotland monthly weather (temperature, sunshine, rainfall) data

Aubinière-Robb et al. Hypertension. 2013;62:190-196.

Temperature sensitivity and mortality



Aubinière-Robb et al. Hypertension. 2013;62:190-196.

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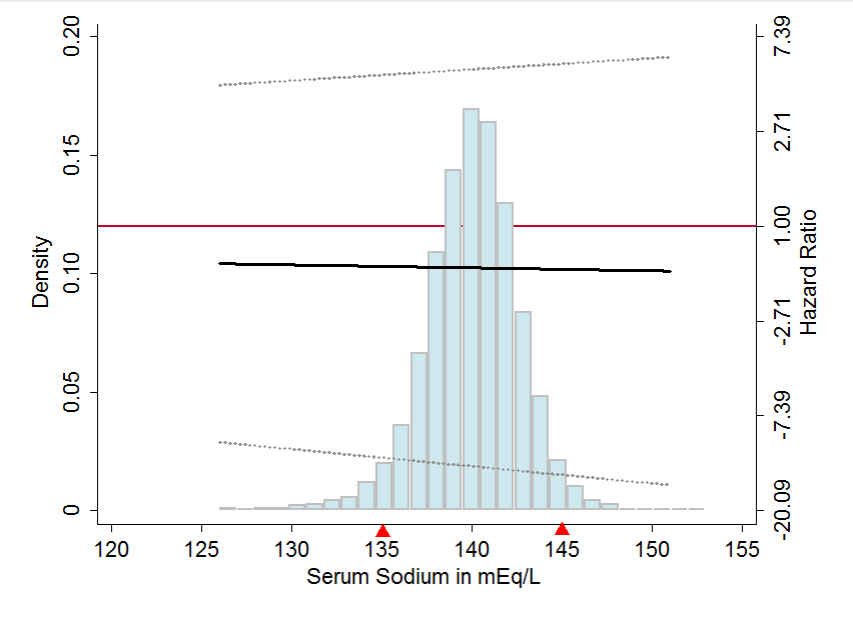
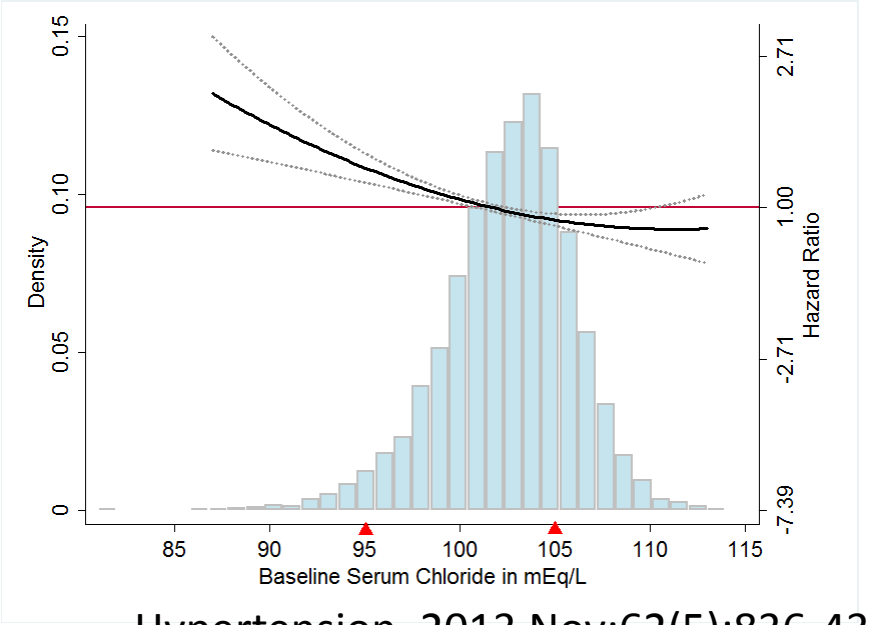
Epidemiology/Population

Serum Chloride Is an Independent Predictor of Mortality in Hypertensive Patients

Linsay McCallum,* Panniyammakal Jeemon,* Claire E. Hastie, Rajan K. Patel, Catherine Williamson, Adyani Md Redzuan, Jesse Dawson, William Sloan, Scott Muir, David Morrison, Gordon T. McInnes, Ellen Marie Freel, Matthew Walters, Anna F. Dominiczak, Naveed Sattar, Sandosh Padmanabhan





Hypertension. 2013 Nov;62(5):836-43

University of Glasgow

European Heart Journal Advance Access published December 15, 2013

European Heart Journal
doi:10.1093/eurheartj/eht539

CLINICAL RESEARCH
Hypertension

Family history of premature cardiovascular disease: blood pressure control and long-term mortality outcomes in hypertensive patients

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Table 2 Family history and risk of mortality

Group	Cox-PH model	All cause death ($n = 3430$)	CV death ($n = 2026$)	IHD death ($n = 1137$)	Stroke death ($n = 480$)	Non-CV death ($n = 1404$)
P-FH$^+$	Model 1	0.74 (0.67–0.81)*	0.77 (0.68–0.87)*	0.84 (0.72–0.99)*	0.70 (0.54–0.91)	0.69 (0.58–0.81)*
	Model 2	0.79 (0.72–0.87)*	0.85 (0.75–0.97)*	0.94 (0.80–1.10)	0.79 (0.61–1.03)	0.70 (0.60–0.83)*
	Model 3	1.14 (1.03–1.26)*	1.23 (1.08–1.39)*	1.34 (1.14–1.58)*	1.19 (0.91–1.55)	1.01 (0.86–1.20)
	Model 4	1.12 (1.01–1.25)*	1.20 (1.04–1.38)*	1.30 (1.08–1.56)*	1.09 (0.80–1.47)	1.00 (0.84–1.20)
		$n = 2991$	$n = 1762$	$n = 1003$	$n = 412$	$n = 1229$
FDR – FH$^+$	Model 1	0.97 (0.89–1.05)	0.99 (0.89–1.10)	1.03 (0.90–1.19)	0.96 (0.78–1.19)	0.95 (0.83–1.08)
	Model 2	1.03 (0.95–1.11)	1.07 (0.96–1.18)	1.12 (0.98–1.29)	1.06 (0.85–1.31)	0.97 (0.85–1.10)
	Model 3	1.16 (1.07–1.26)*	1.20 (1.08–1.33)*	1.27 (1.10–1.46)*	1.19 (0.96–1.46)	1.09 (0.96–1.24)
	Model 4	1.11 (1.02–1.22)*	1.14 (1.01–1.28)*	1.17 (1.01–1.38)*	1.09 (0.85–1.41)	1.07 (0.93–1.24)
		$n = 887$	$n = 526$	$n = 309$	$n = 108$	$n = 361$
P-FH$^+$	Propensity matched	1.15 (1.00–1.32)*	1.28 (1.07–1.53)*	1.40 (1.12–1.77)*	1.23 (0.83–1.81)	0.98 (0.79–1.22)

European Heart Journal (2016) **37**, 968–974
doi:10.1093/eurheartj/ehv557

CLINICAL RESEARCH
Hypertension

Contrasting mortality risks among subgroups of treated hypertensive patients developing new-onset diabetes

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Received 15 April 2015; revised 10 August 2015; accepted 29 September 2015; online publish-ahead-of-print 27 October 2015

See page 975 for the editorial comment on this article (doi:10.1093/eurheartj/ehv594)

European Heart Journal (2016) **37**, 975–977
doi:10.1093/eurheartj/ehv594

EDITORIAL

New-onset diabetes in hypertensive patients and mortality: timing is everything

Rosa Maria Bruno[1,2] and Stefano Taddei[1]*

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; and [2]Institute of Clinical Physiology, CNR, Pisa, Italy

Online publish-ahead-of-print 9 November 2015

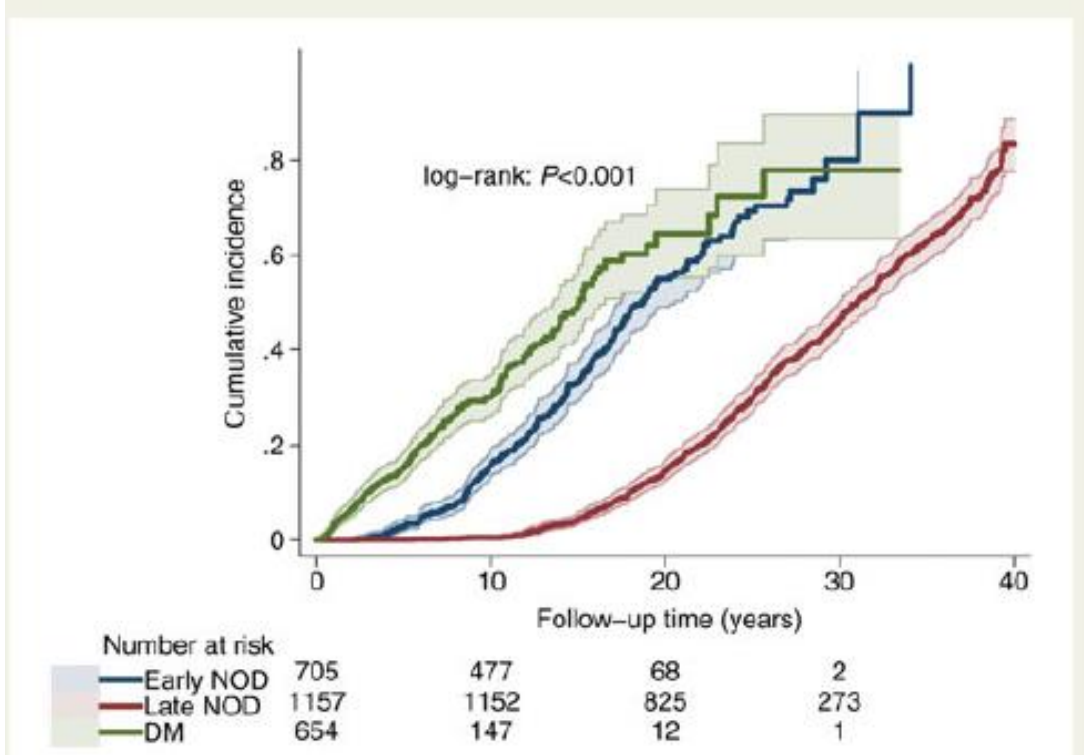
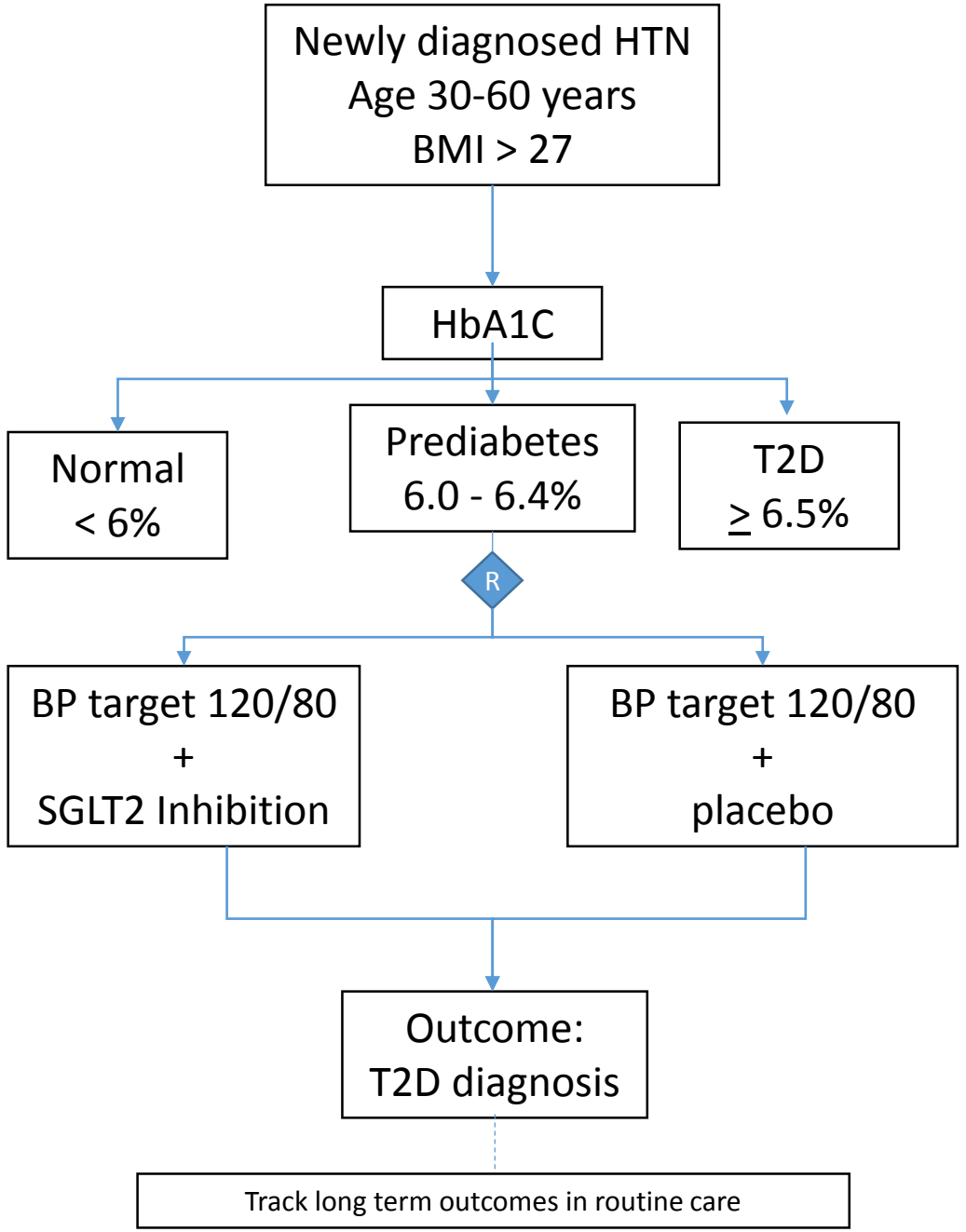


Figure 2 Survival analysis (time to all-cause mortality) of early and late NOD. NOD, new-onset diabetes; early NOD, those who developed diabetes within the first 10-year follow-up; late NOD, those who developed after completion of 10-year follow-up.


Newly diagnosed HTN
Age 30-60 years
BMI > 27
HbA1C
Normal
< 6%
Prediabetes
6.0 - 6.4%
T2D
≥ 6.5%
R
BP target 120/80
+
SGLT2 Inhibition
BP target 120/80
+
placebo
Outcome:
T2D diagnosis
Track long term outcomes in routine care

University of Glasgow

Epidemiology/Population

OPEN

Monotherapy With Major Antihypertensive Drug Classes and Risk of Hospital Admissions for Mood Disorders

Angela H. Boal, Daniel J. Smith, Linsay McCallum, Scott Muir, Rhian M. Touyz, Anna F. Dominiczak, Sandosh Padmanabhan

Abstract—Major depressive and bipolar disorders predispose to atherosclerosis, and there is accruing data from animal model, epidemiological, and genomic studies that commonly used antihypertensive drugs may have a role in the pathogenesis or course of mood disorders. In this study, we propose to determine whether antihypertensive drugs have an impact on mood disorders through the analysis of patients on monotherapy with different classes of antihypertensive drugs from a large hospital database of 525 046 patients with follow-up for 5 years. There were 144 066 eligible patients fulfilling the inclusion criteria: age 40 to 80 years old at time of antihypertensive prescription and medication exposure >90 days. The burden of comorbidity assessed by Charlson and Elixhauser scores showed an independent linear association with mood disorder diagnosis. The median time to hospital admission with mood disorder was 847 days for the 299 admissions (641 685 person-years of follow-up). Patients on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers had the lowest risk for mood disorder admissions, and compared with this group, those on β-blockers (hazard ratio=2.11; [95% confidence interval, 1.12–3.98]; *P*=0.02) and calcium antagonists (2.28 [95% confidence interval, 1.13–4.58]; *P*=0.02) showed higher risk, whereas those on no antihypertensives (1.63 [95% confidence interval, 0.94–2.82]; *P*=0.08) and thiazide diuretics (1.56 [95% confidence interval, 0.65–3.73]; *P*=0.32) showed no significant difference. Overall, our exploratory findings suggest possible differential effects of antihypertensive medications on mood that merits further study: calcium antagonists and β-blockers may be associated with increased risk, whereas angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may be associated with a decreased risk of mood disorders. **(*Hypertension*. 2016;68:1132-1138. DOI: 10.1161/HYPERTENSIONAHA.116.08188.)** • **Online Data Supplement**

University of Glasgow

Monotherapy With Major Antihypertensive Drug Classes and Risk of Hospital Admissions for Mood Disorders

Angela H. Boal, Daniel J. Smith, Linsay McCallum, Scott Muir, Rhian M. Touyz, Anna F. Dominiczak, Sandosh Padmanabhan

Monotherapy With Major Antihypertensive Drug Classes and Risk of Hospital Admissions for Mood Disorders

Overview of attention for article published in Hypertension (Highwire), January 2016

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Title	Monotherapy With Major Antihypertensive Drug Classes and Risk of Hospital Admissions for Mood Disorders
Published in	Hypertension (Highwire), January 2016
DOI	10.1161/hypertensionaha.116.08188
Pubmed ID	27733585
Authors	Angela H. Boal, Daniel J. Smith, Linsay McCallum, Scott Muir, Rhian M. Touyz, Anna F. Dominiczak... [show]
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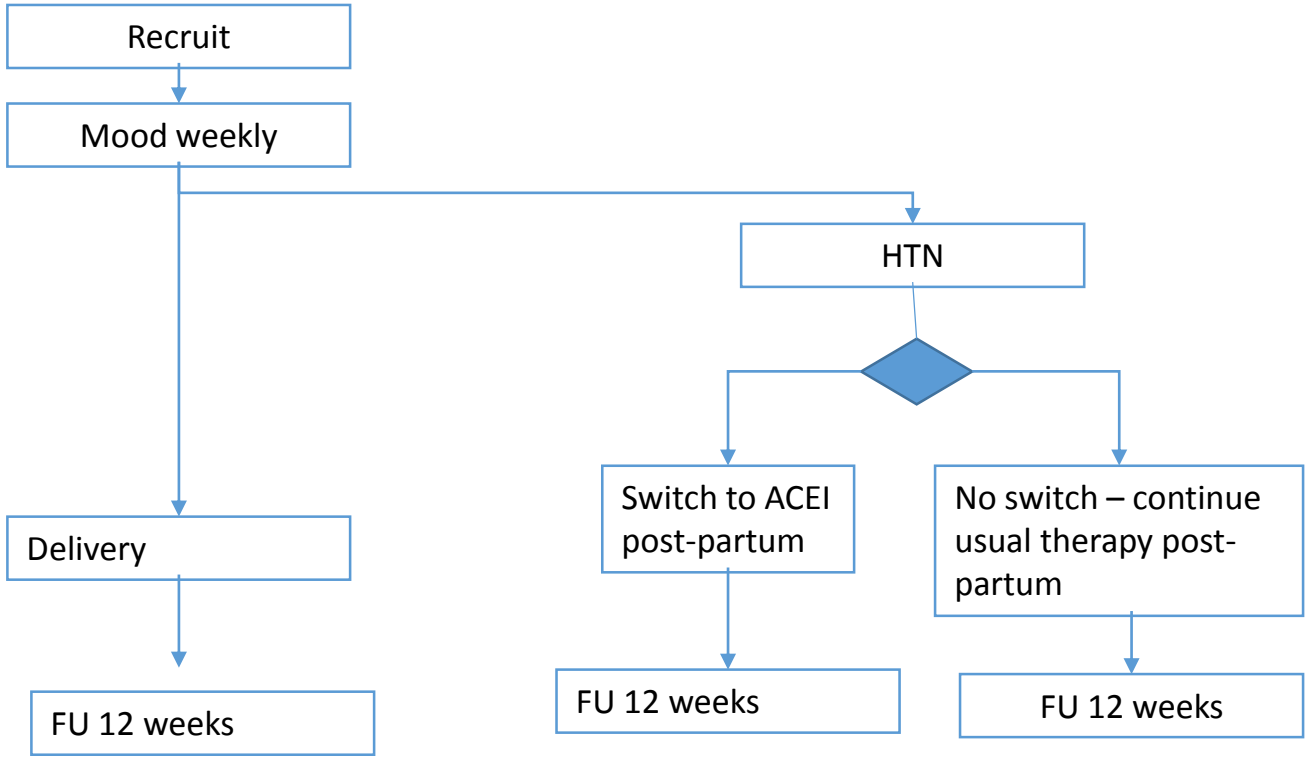
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Mood weekly
HTN
Delivery
Switch to ACEI post-partum
No switch – continue usual therapy post-partum
FU 12 weeks
FU 12 weeks
FU 12 weeks

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