From Low Birth Weight to CAKUT Implications for Adulthood

Robert L. Chevalier, MD, FASN
Professor Emeritus
Department of Pediatrics
University of Virginia
Charlottesville, Virginia, USA

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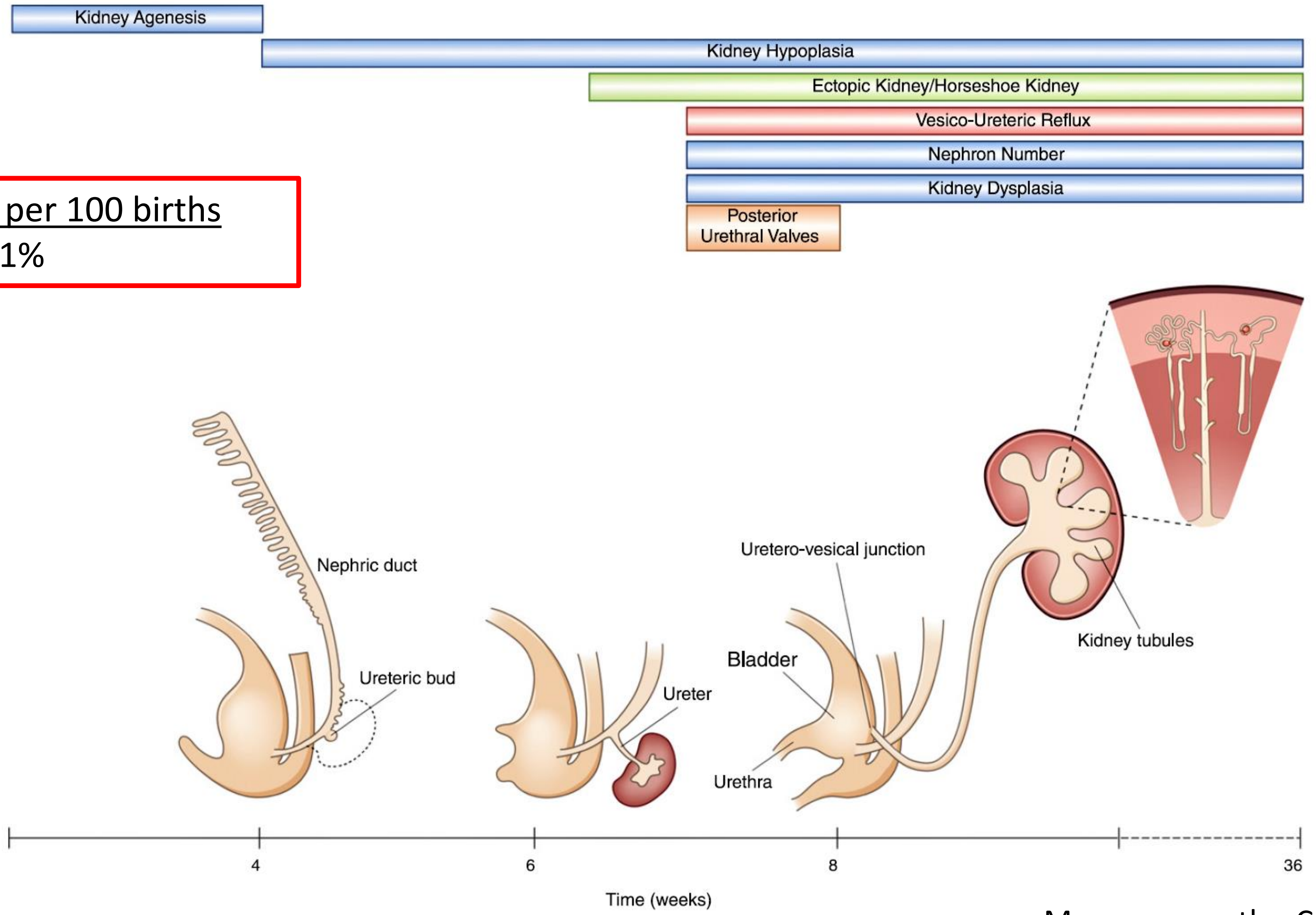
Normal & abnormal kidney development



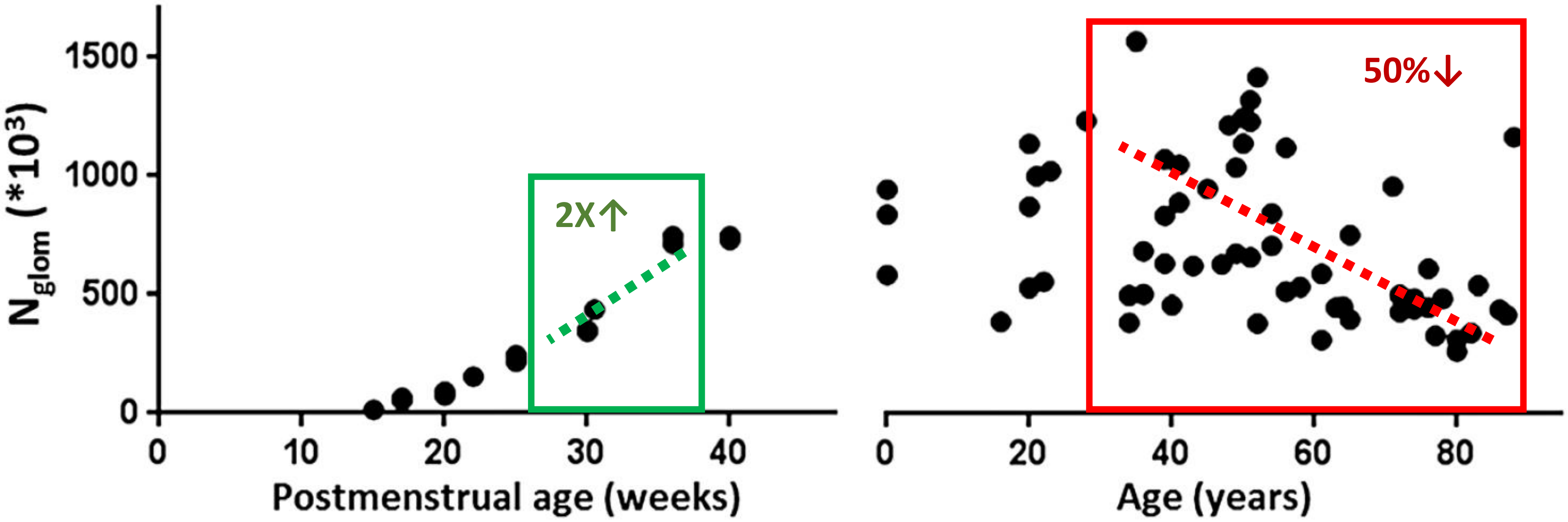
<u>Prevalence per 100 births</u>

CAKUT <1%

Murugapoopathy. CJASN 15:723-731, 2020

Blencoe. Lancet 2019

Determinants of nephron number over life span



Genetic	Prenatal (prematurity)		Pediatric	Adult
RET PAX2 ACE OSR1 ALDH1A2	Nutrition IUGR Iron deficiency Vitamin A deficiency Vitamin D status Hyperglycemia Ethanol	Tobacco Medications -cyclosporine -ACEI -NSAIDs -aminoglycosides	Nutrition AKI Medications Chronic illnesses Hypertension	Diabetes Hypertension Autoimmune diseases UTI Urinary tract obstruction AKI Medications

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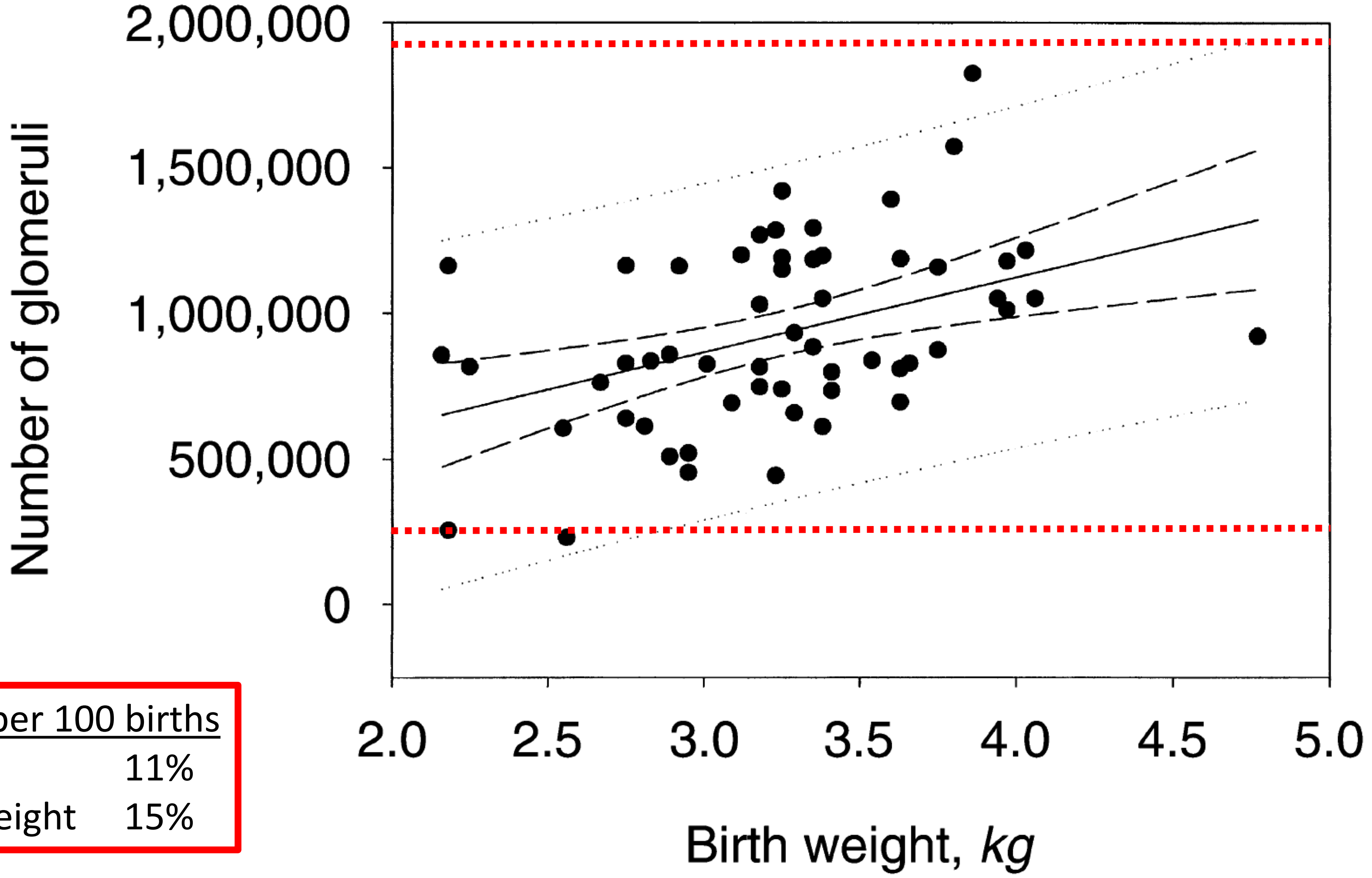
Charlton Ped Nephrol 2014

10-fold variation in nephron number at birth: Nephron number is correlated with birth weight



Prevalence per 100 births	
Prematurity	11%
Low birth weight	15%

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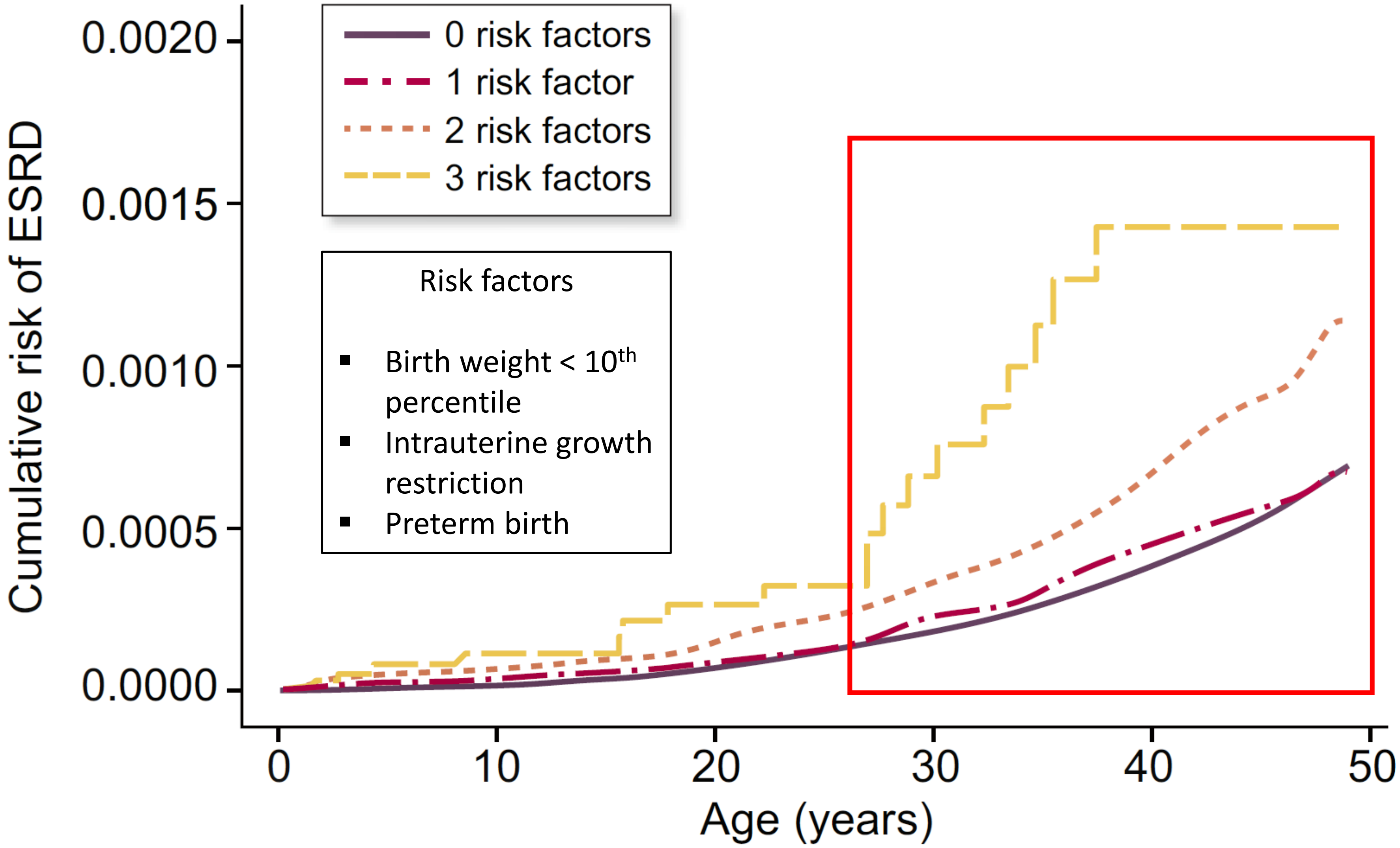
Hughson M et al. Kidney Int 63:2113, 2003

Low birth weight, IUGR, and preterm birth are risk factors for ESRD in adulthood

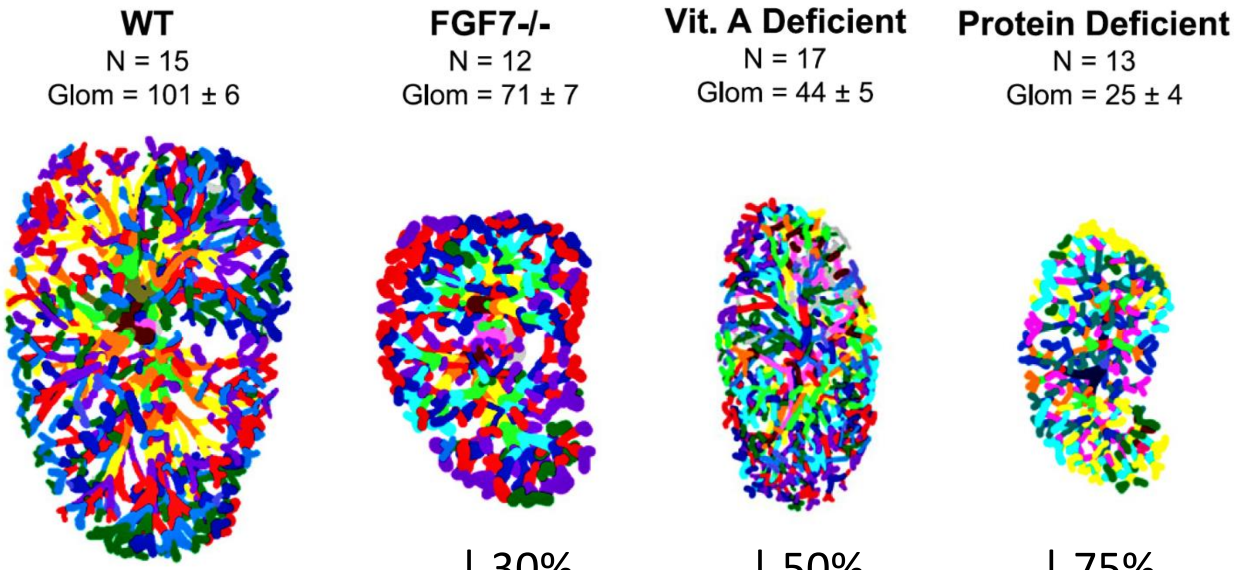


Gjerde. Nephrol Dial Transp 35:1157, 2020

Developmental programming of kidney branching morphogenesis

Maternal nutrient deficiency→ ↓nephron number

Micronutrient   Macronutrient



↓30%   ↓50%   ↓75%

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Sampogna. JASN 25:2414, 2015

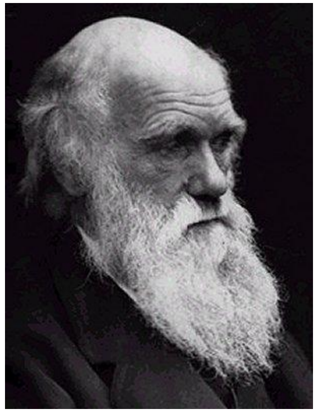
Current paradigm

Low nephron number is a major risk factor leading to CKD in postnatal life.

A maladaptive developmental response?

An evolutionary adaptation to the environment?

- **Evolution: selection driven by energy**
- **Maternal-fetal signaling: epigenetics**
- **Ancestry of metabolic pathways**
- **Metabolic control of nephrogenesis**
- **Research and clinical implications**



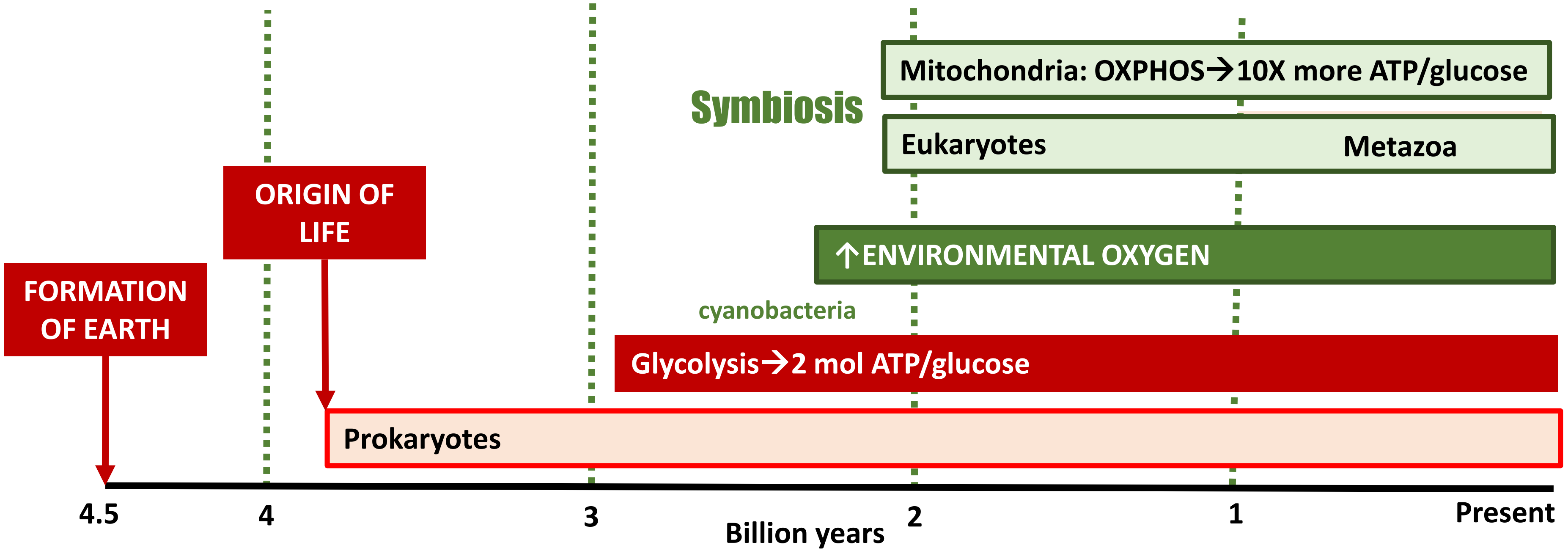
The Theory of Evolution by Natural Selection

Proposed in 1859 by Charles Darwin to explain the diversity and exquisite adaptations exhibited by life on earth

- Existence of inter-individual variation within any population
- Selection by the environment for fittest organisms which then differentially reproduce
- Heritability of variations

Energy is the driver of evolutionary complexity

Natural selection is constrained by available energy



ADAPTATION TO ENVIRONMENT

OXPHOS →10X more ATP/glucose than glycolysis

Tradeoff: Mitochondrial OXPHOS → ↑ROS

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Energy reallocation→ large brain buffers starvation

Available energy is allocated through life cycle, selected for increasing fitness:

- **Growth**
- **Reproduction**
- **Immune response**
- **Maintenance**

Small brain

Big jaw

Homo habilis

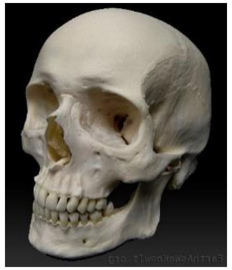
2 million years ago

CLIMATE CHANGE IN EAST AFRICA

↑ nutrient availability

Big brain

Small jaw

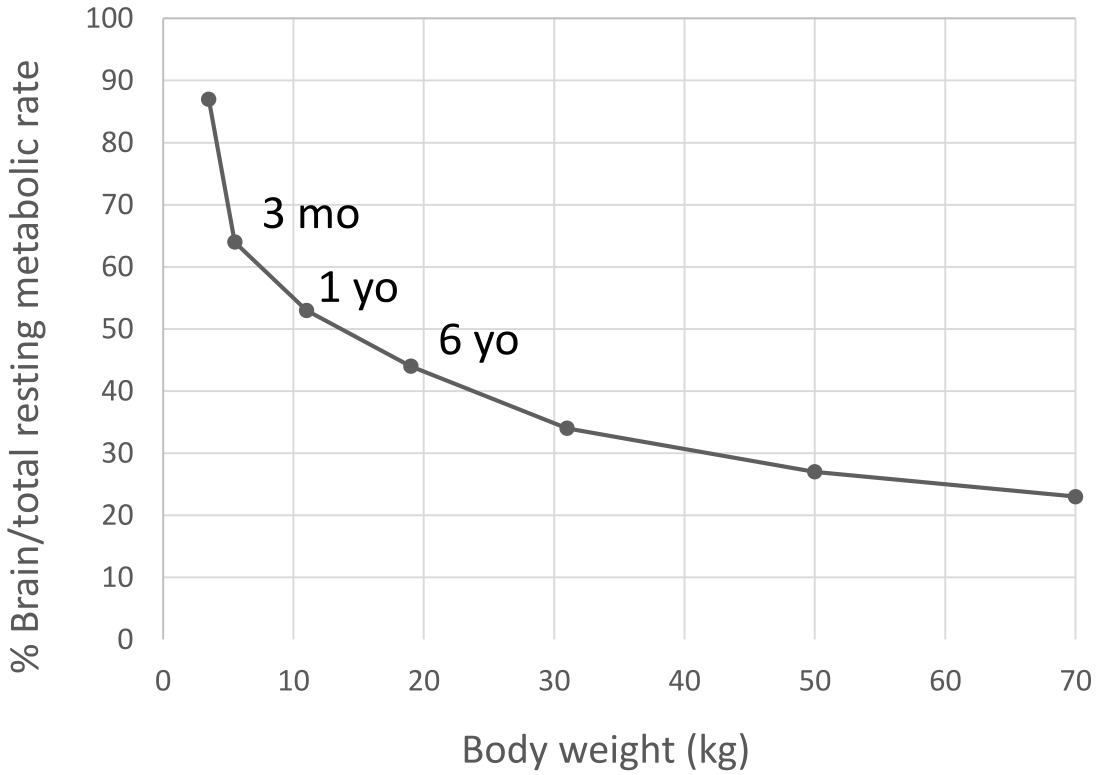


Homo sapiens

<u>Tradeoff</u>: developing kidney energy consumption must be balanced with priority of energy allocation to brain

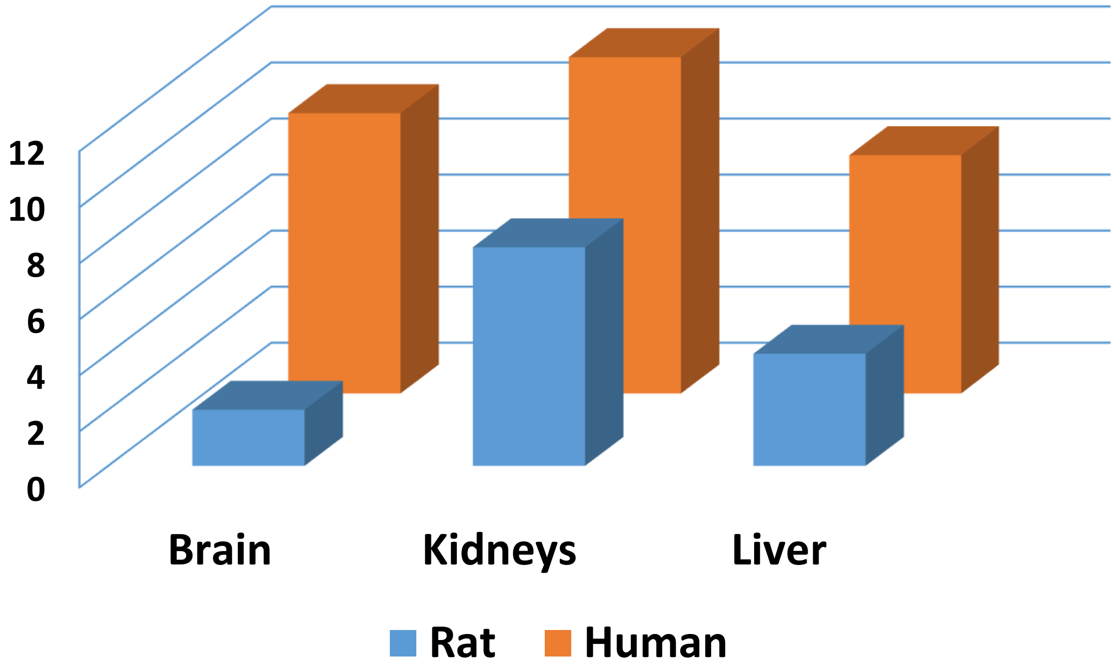
Navarrete. Nature 480:91. 2011

Inter-organ competition for available energy



Data from MA Holliday in Falkner & Tanner: Human Growth, vol. 2, 2nd ed. 1986

Adult oxygen Consumption Index ($\%O_2$ consumption/% body mass)



Rolfe & Brown. Physiol Rev77:731, 1997

Maternal-Fetal Conflict
(natural selection is driven by reproductive fitness)

Pregnancy & breastfeeding→20% ↑energy requirement

In response to maternal undernutrition, the fetus can reduce its energy consumption by

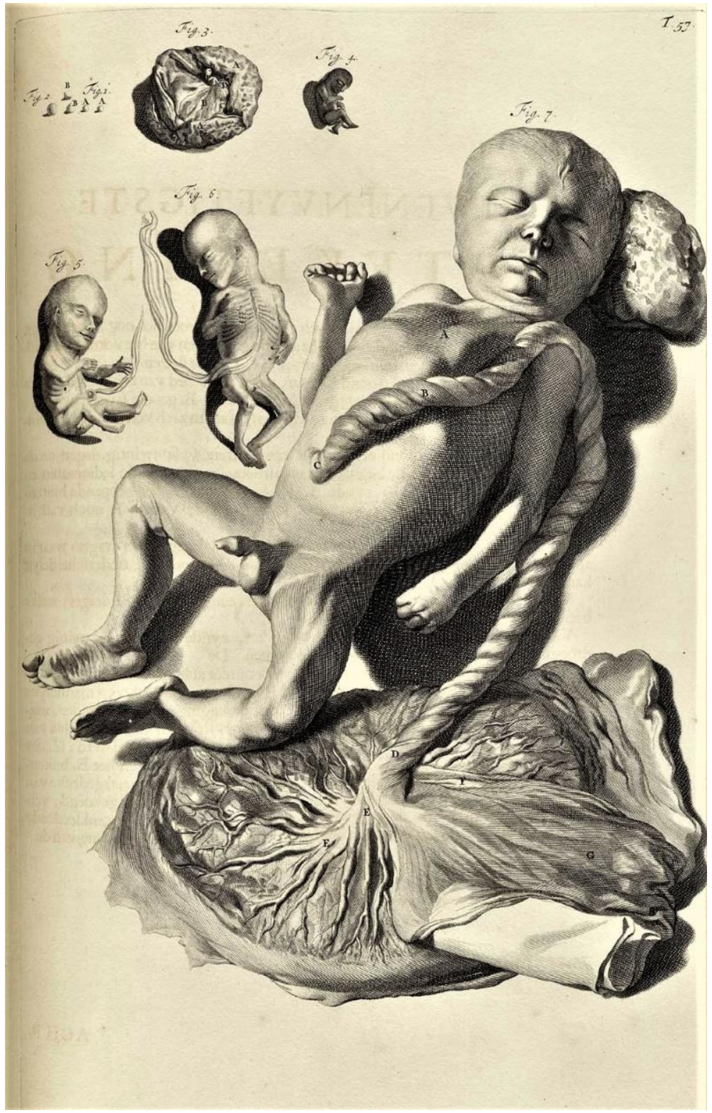
- Slowed somatic growth (IUGR)
- Accelerated maturation through cortisol release and premature delivery
- Death

Gluckman & Hanson *The Fetal Matrix* 2005

Placenta—made by fetus, favors mother

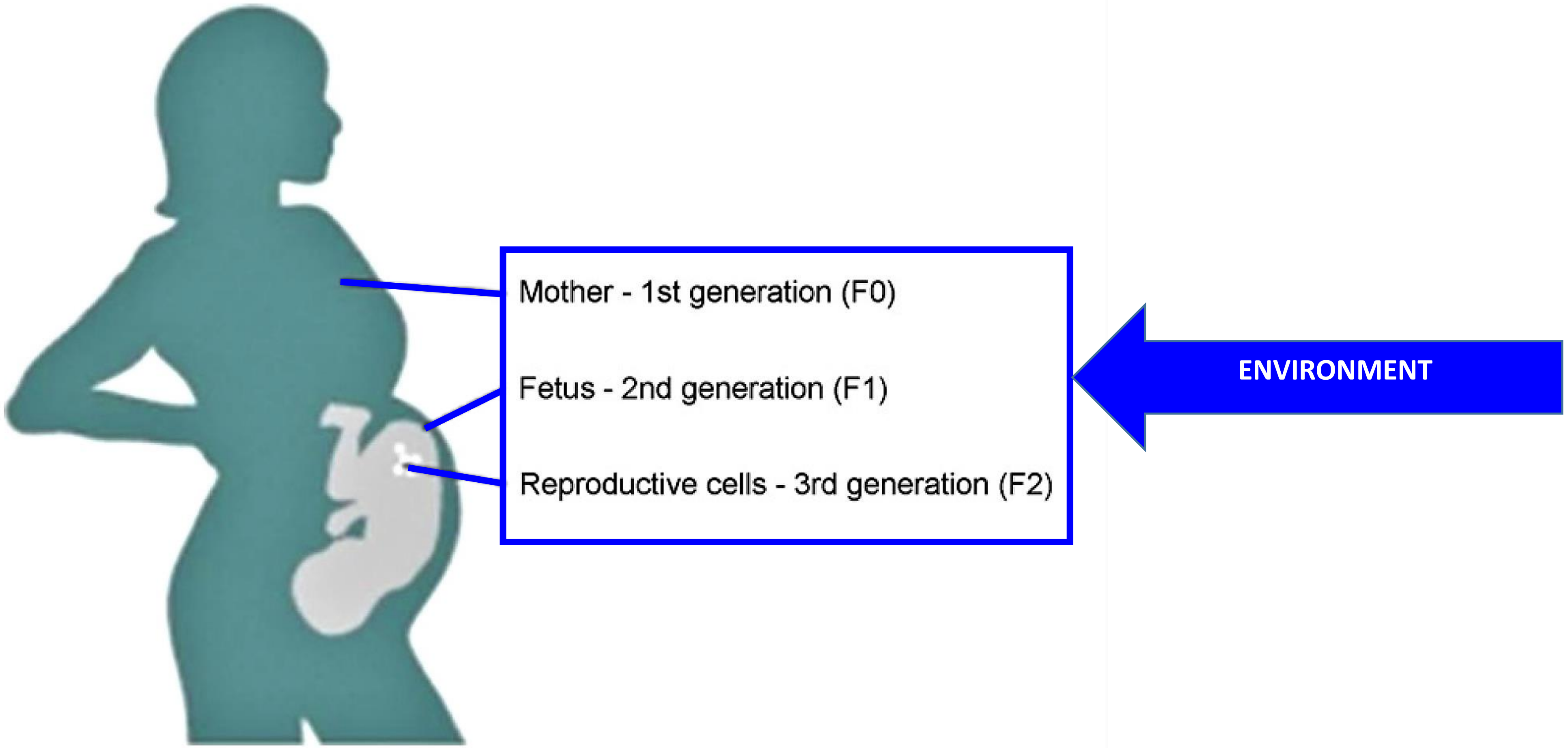
- Balances energy resources and needs of mother vs. fetus
- Restricted maternal nutrition favors fitness of mother: having reached reproductive age, she is more likely to reproduce in the future

Lewis, Cleal, Hanson. Placenta 33 Suppl A. 26:S28-S32, 2012



Govaert Bidloo. 1690

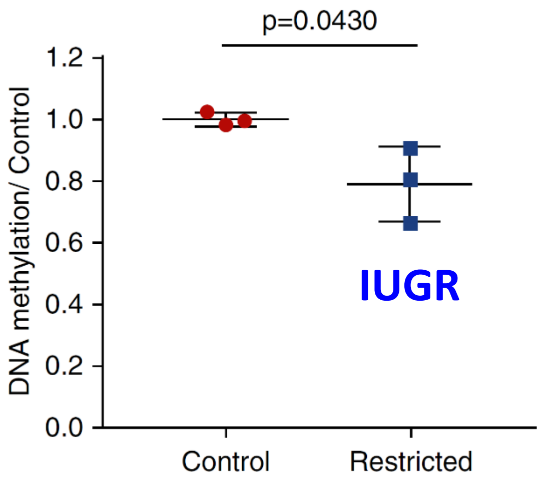
Epigenetics: intergenerational inheritance

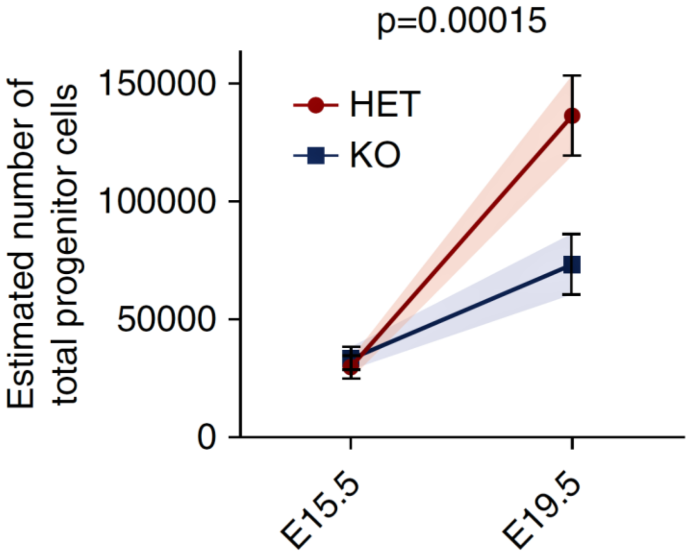


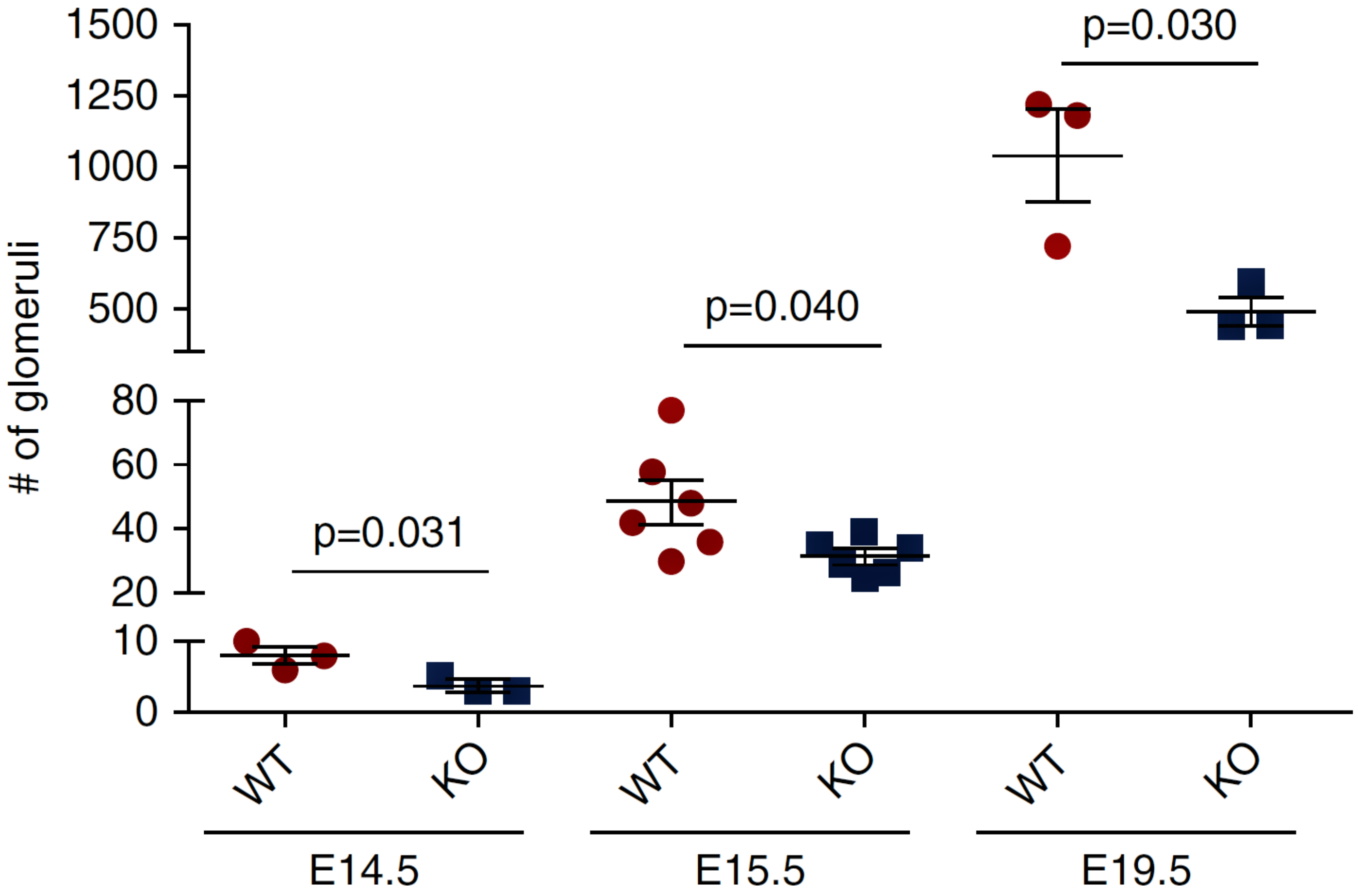
Barker. Placenta 33 Suppl 2:e30-4, 2012

Perera & Herbstman. Repro Toxicol 31:363, 2011

EPIGENETICS: DNA methyltransferase1 activity Determinant of nephron number in mouse kidney







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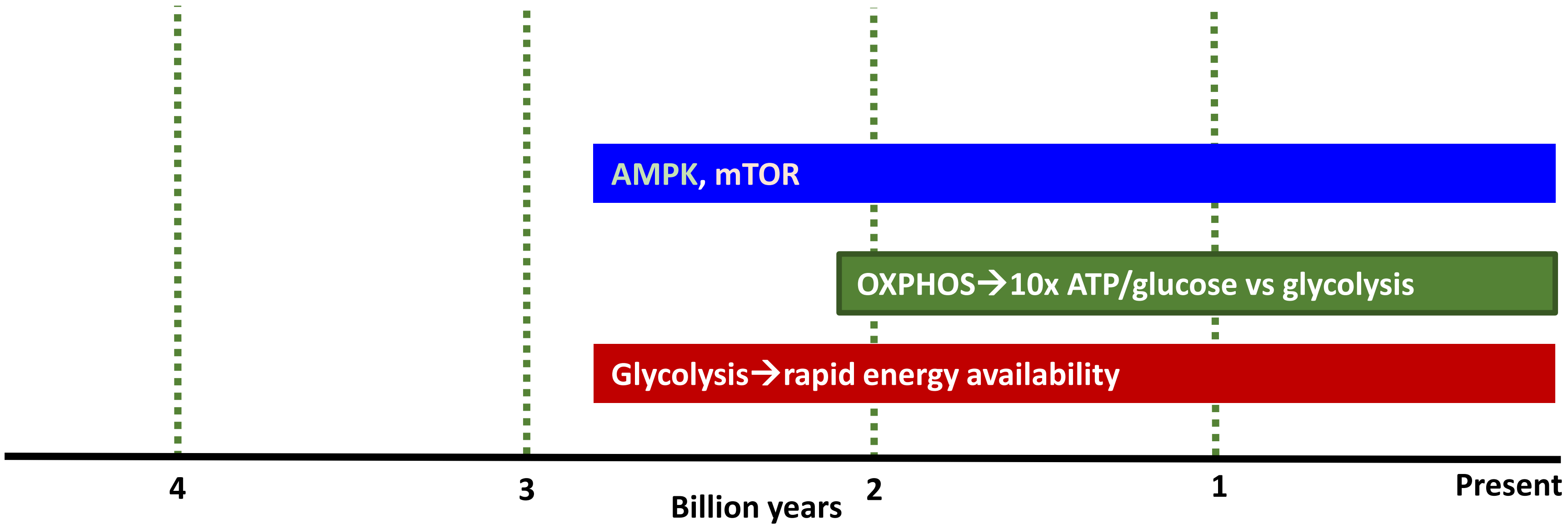
Wanner JASN 30:63, 2019

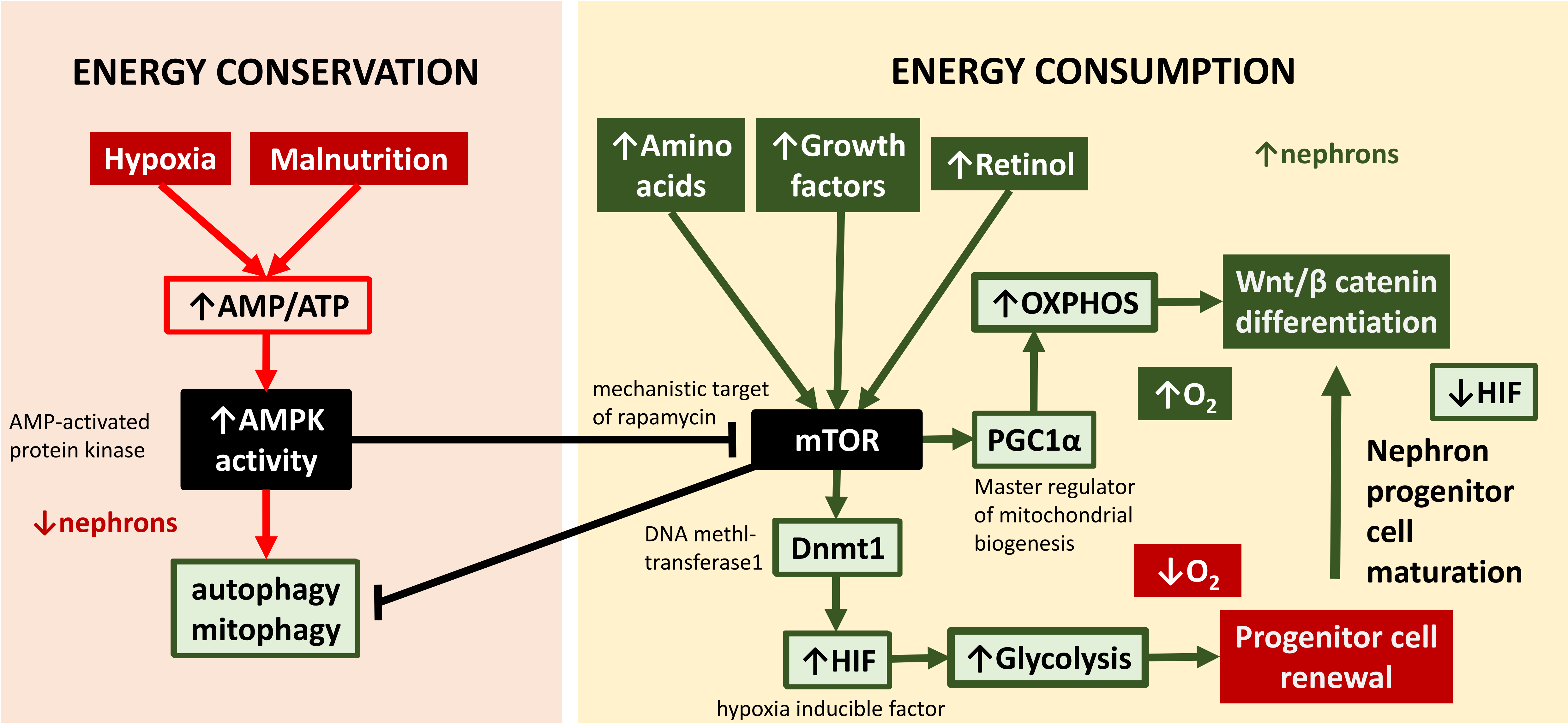
Metabolic reprogramming → developmental plasticity

Glycolysis ⟷ OXPHOS



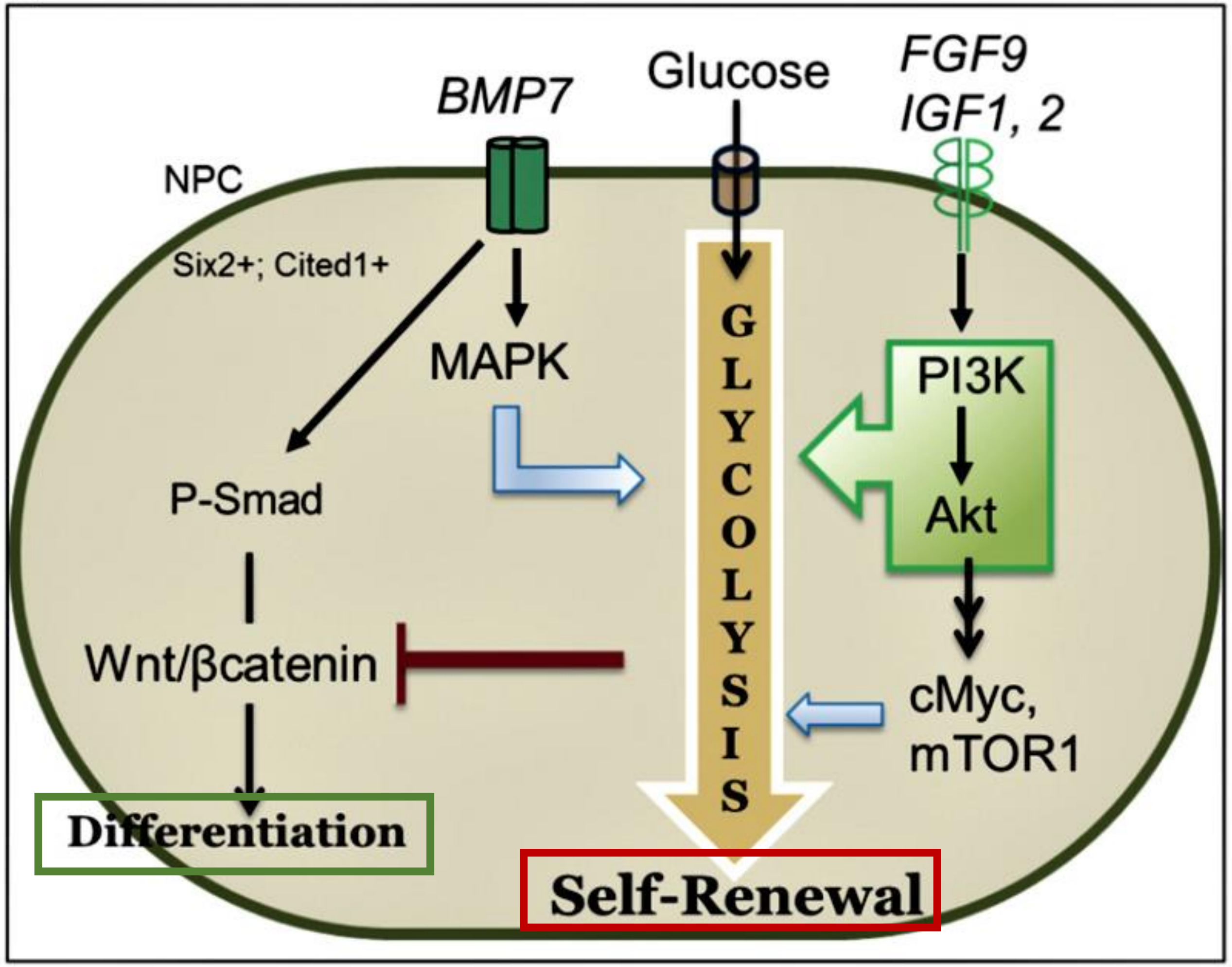
AMP-activated protein kinase
mechanistic target of rapamycin

Oxygen and nutrient availability determine fetal nephron number through counterbalancing mechanisms



Metabolic reprogramming determines renal progenitor cell fate

↑O_2

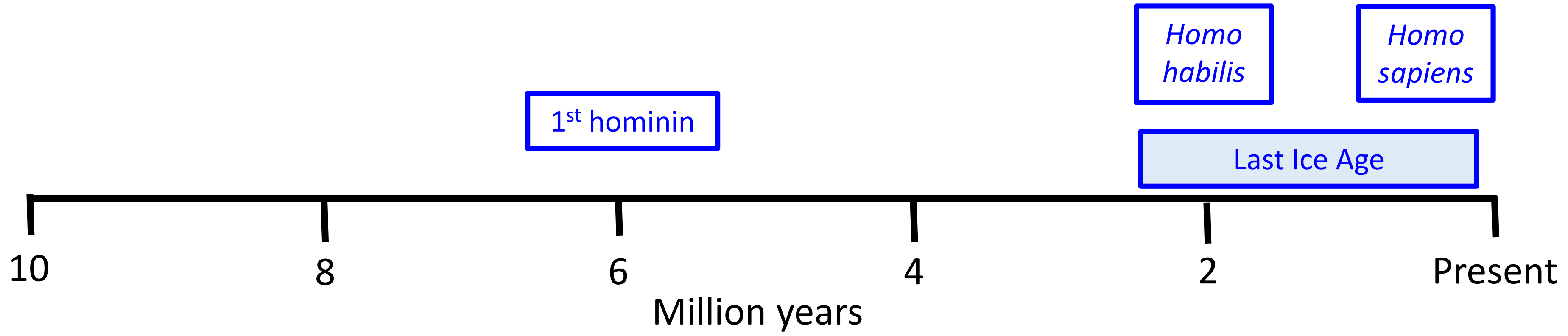


↓O_2

Liu JASN 28:3323, 2017

ORIGINS: Energy conservation

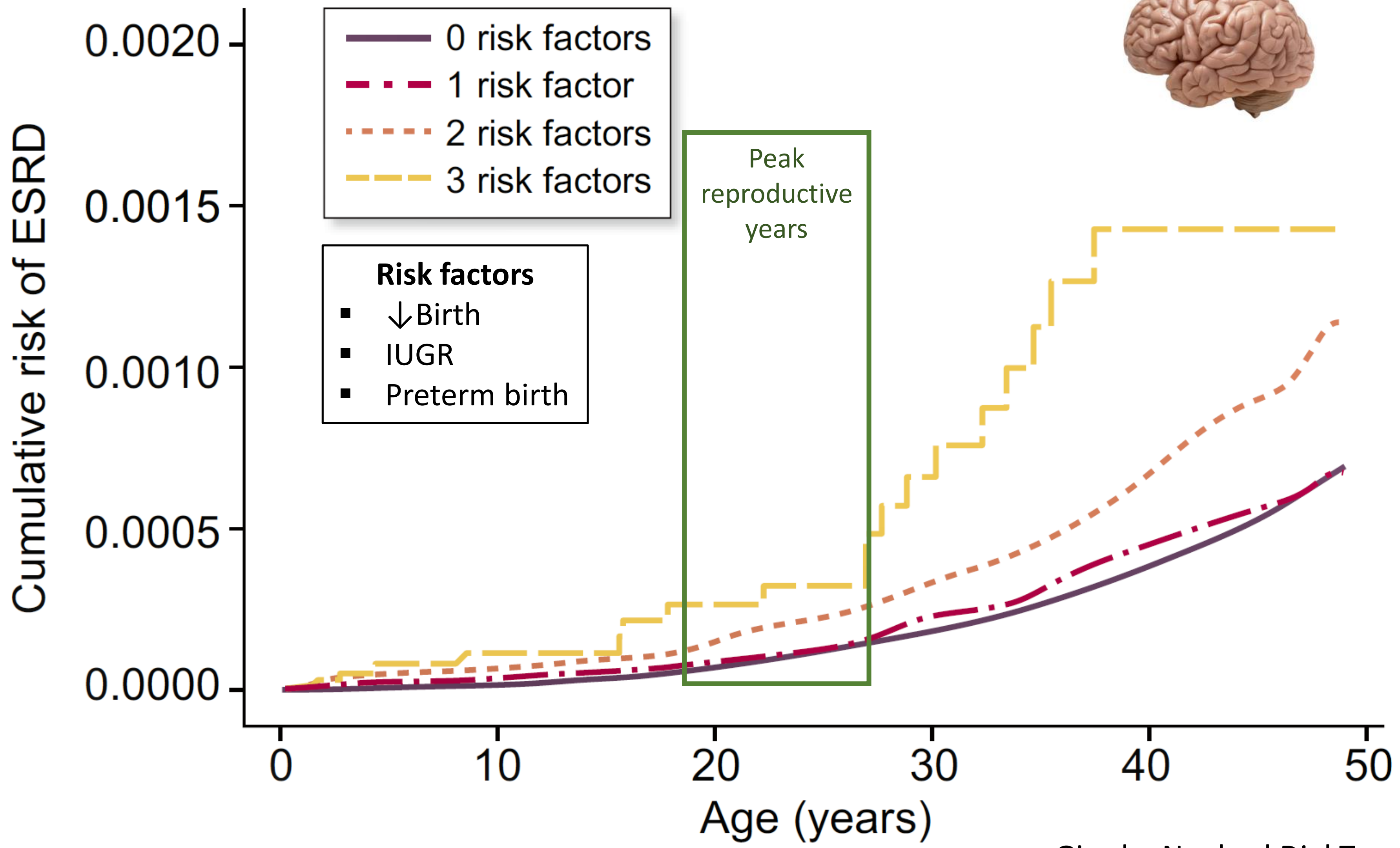
- Energy available to the organism is constrained by the environment, and its distribution is constrained by evolutionary history.
- This history reflects our prokaryotic ancestry dating back **3 billion years**, when metabolic AMPK and TOR signaling evolved.
- In response to environmental pressures over the past **2 million years,** selection favored a large brain with high energy consumption.



Genetic and epigenetic adaptations to the environment

- Maternal energy restriction is signaled to the placenta and fetus by reduced nutrients or hypoxia that activate AMPK and suppress mTOR.
- Maternal nutrition signals nephron progenitor cells through DNA methylation by Dnmt, an epigenetic pathway conserved over 800 million years.
- Nephron progenitor cells proliferate through glycolytic metabolism.
- Increased environmental oxygen suppresses HIF1, reprogramming to OXPHOS metabolism and nephron differentiation.

Restricted maternal energy signals reduced nephrogenesis, allocating energy to fetal brain growth, a life history strategy favoring reproductive fitness but risk for CKD in adulthood



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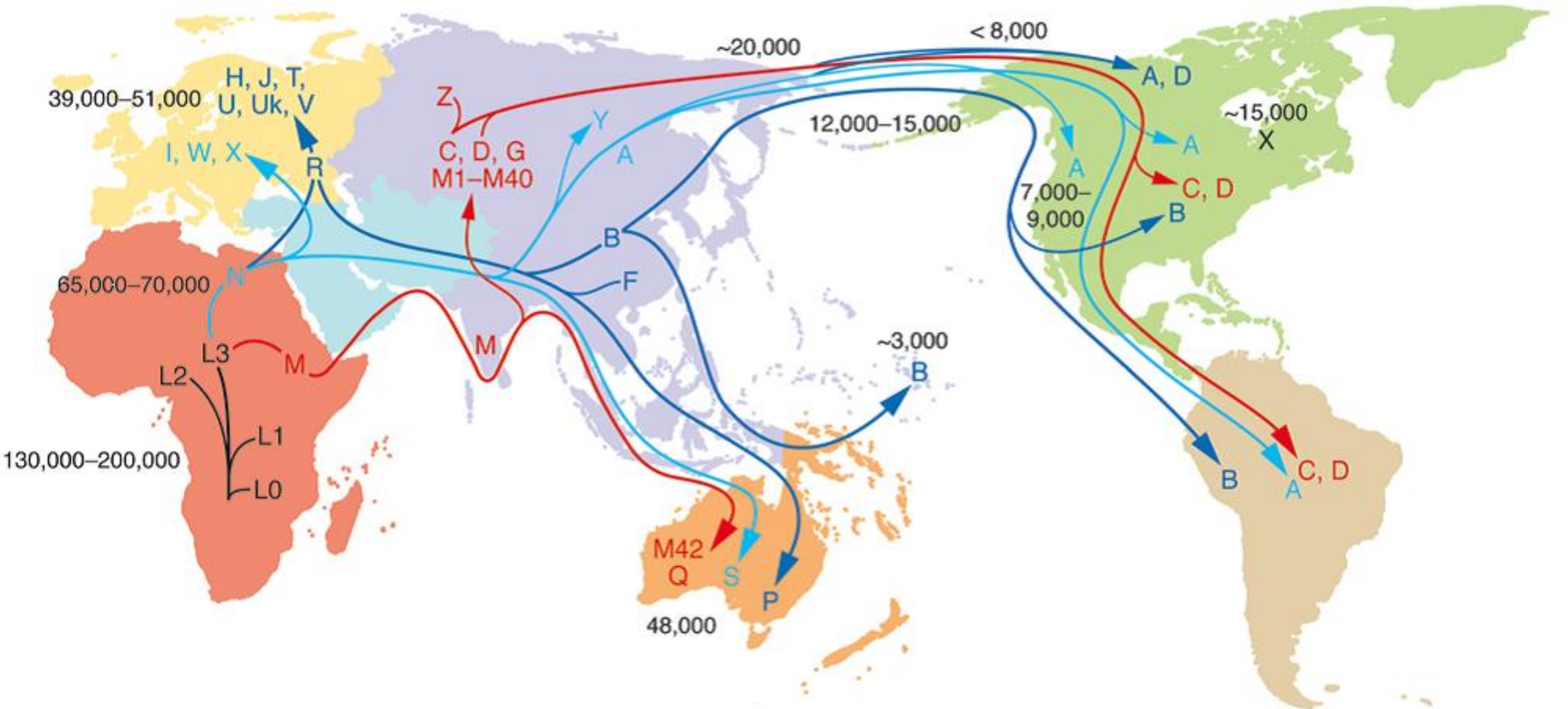
Gjerde. Nephrol Dial Transp 35:1157, 2020

Homo sapiens: Dispersion of mitochondrial haplogroups over 70,000 years



Wallace. J Clin invest 123:1405, 2013

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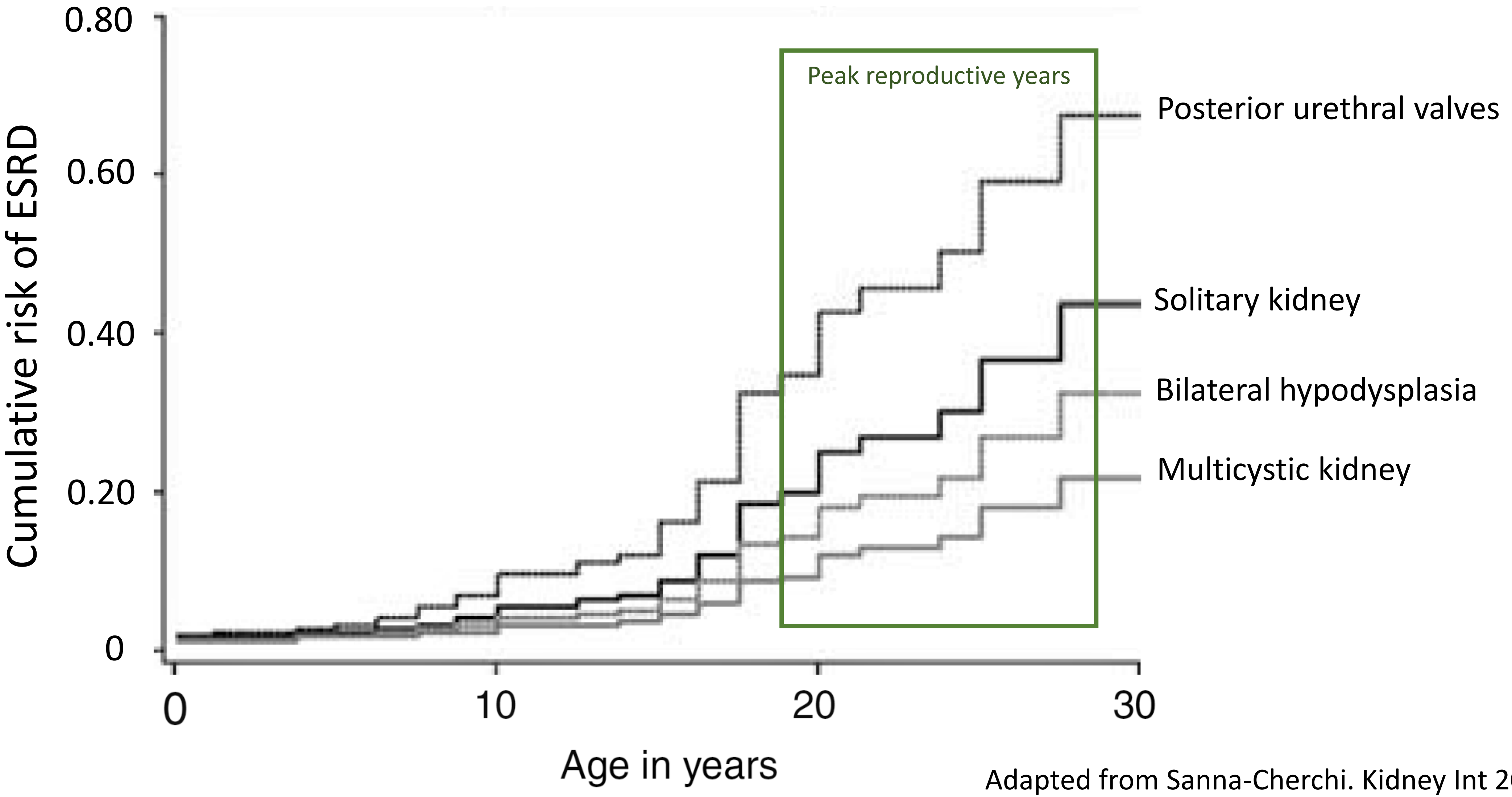
Severe impairment of nephrogenesis (CAKUT) cannot maintain metabolic balance through adolescence, with increasing risk for ESRD in peak reproductive years



Adapted from Sanna-Cherchi. Kidney Int 2009

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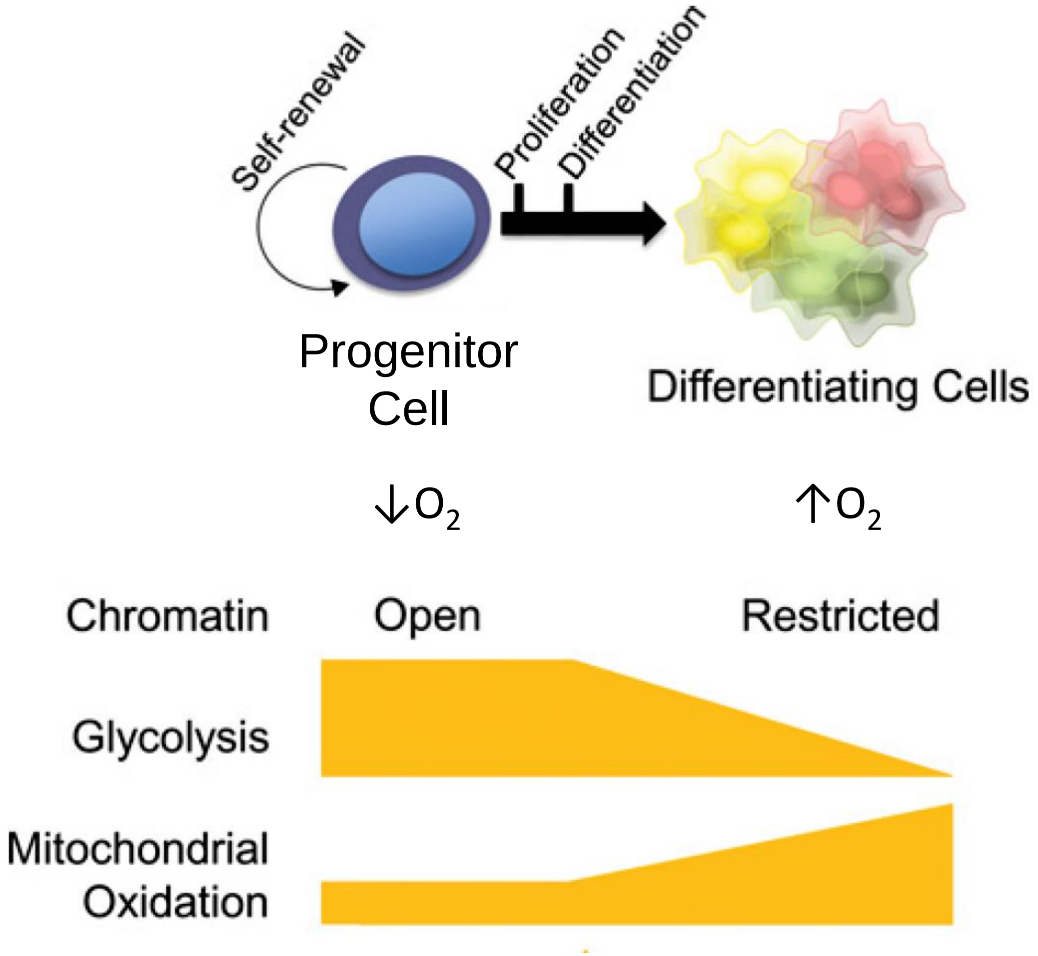
Future research on nephrogenesis:
Focus on metabolism and epigenetic signaling

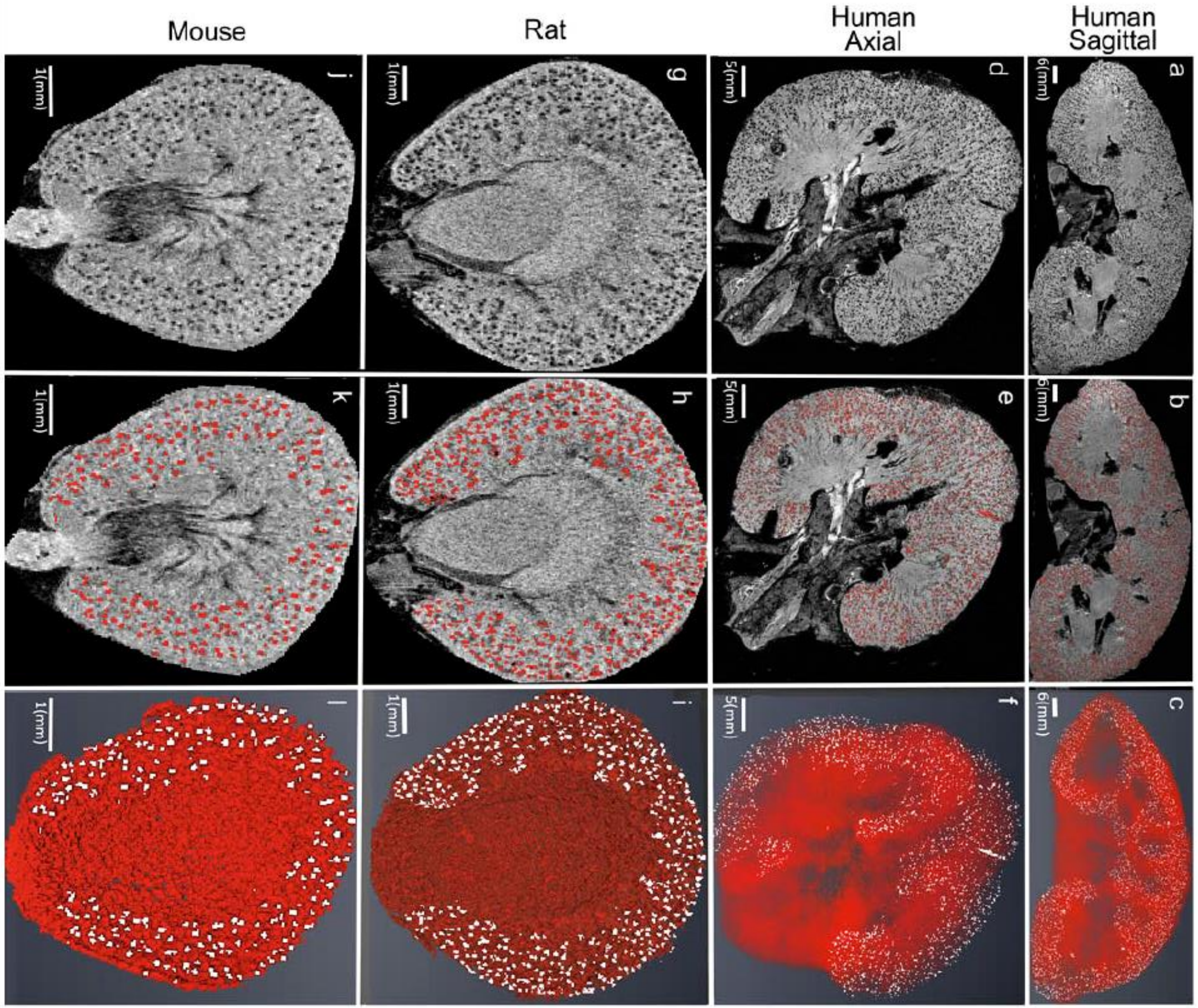


Epigenetic signaling

Metabolic reprogramming

Shyh-Chang. Genes Dev 31:336, 2017

The Future: In vivo measurement of nephron number

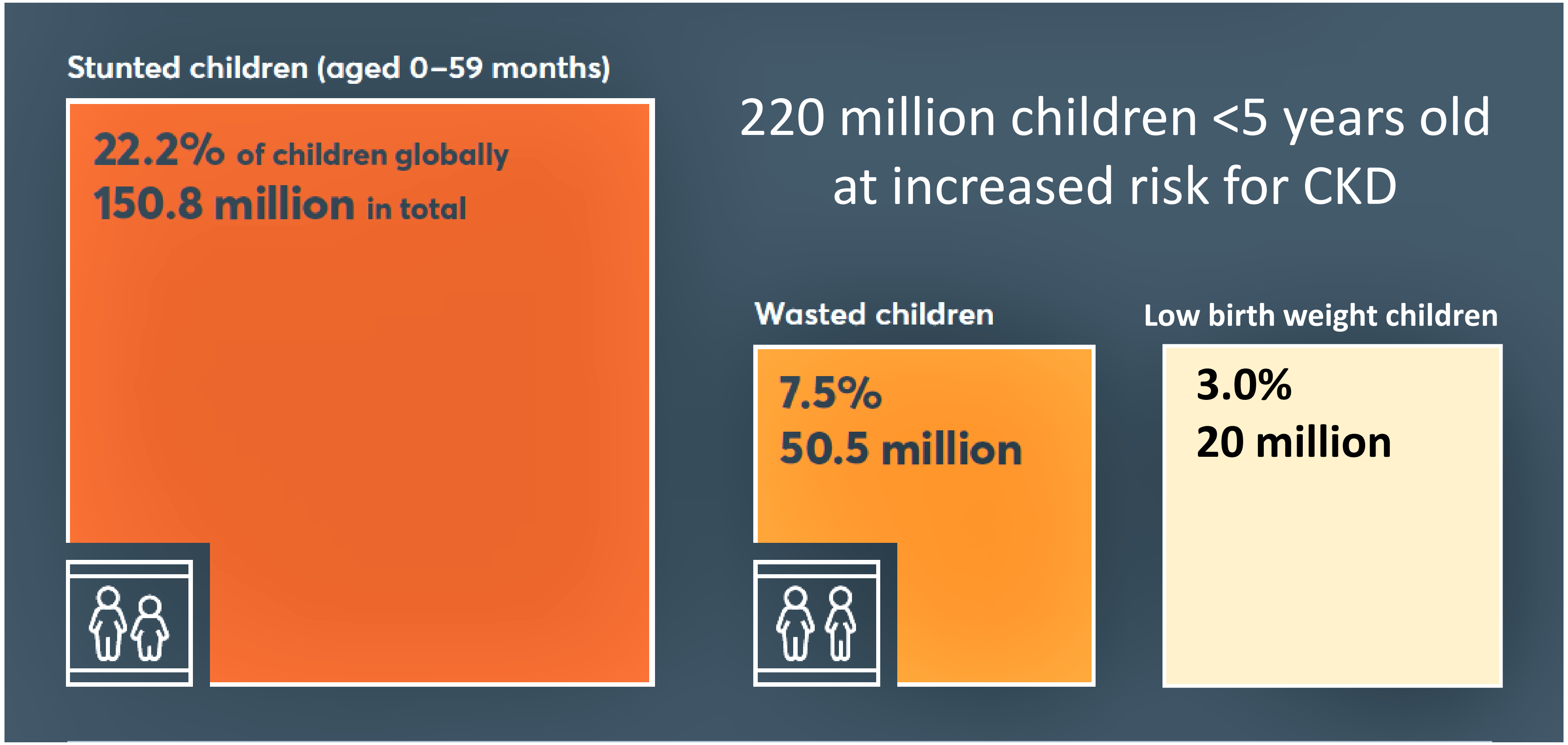


Cationic ferritin - enhanced magnetic resonance imaging

Charlton. Ped Nephrol 2020

Public health implications for the future

- Accelerating climate change and increasing global malnutrition in children will predictably lead to a rising prevalence of CKD.
- Optimizing maternal-child health should receive high priority across the globe.



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https://globalnutritionreport.org/reports/global-nutrition-report-2018/

For More Information—New ASN Journal

Review Article Kidney360

Bioenergetic Evolution Explains Prevalence of Low Nephron Number at Birth: Risk Factor for CKD

Robert L. Chevalier
RLC2M@virginia.edu

KIDNEY360 1: 863–879, 2020.

https://kidney360.asnjournals.org/content/1/8/863