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
Prevalence per 100 births
CAKUT <1%

Murugapoopathy. CJASN 15:723-731, 2020
Blencoe. Lancet 2019
Determinants of nephron number over life span

- Postmenstrual age vs. Glomerulus count
- Age vs. Nephron number

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Prenatal (prematurity)</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET</td>
<td>Nutrition</td>
<td>Tobacco</td>
<td>Diabetes</td>
</tr>
<tr>
<td>PAX2</td>
<td>IUGR</td>
<td>Medications</td>
<td>Hypertension</td>
</tr>
<tr>
<td>ACE</td>
<td>Iron deficiency</td>
<td>-cyclosporine</td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td>OSR1</td>
<td>Vitamin A deficiency</td>
<td>-ACEI</td>
<td>UTI</td>
</tr>
<tr>
<td>ALDH1A2</td>
<td>Vitamin D status</td>
<td>-NSAIDs</td>
<td>Urinary tract obstruction</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>-aminoglycosides</td>
<td>AKI</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
<td></td>
<td>Medications</td>
</tr>
</tbody>
</table>
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%

Low birth weight, IUGR, and preterm birth are risk factors for ESRD in adulthood.
Developmental programming of kidney branching morphogenesis

Maternal nutrient deficiency $\rightarrow$ ↓nephron number

- WT
  - N = 15
  - Glom = 101 ± 6

- FGF7-/-
  - N = 12
  - Glom = 71 ± 7
  - ↓30%

- Vit. A Deficient
  - N = 17
  - Glom = 44 ± 5
  - ↓50%

- Protein Deficient
  - N = 13
  - Glom = 25 ± 4
  - ↓75%
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
Energy reallocation ➔ large brain buffers starvation

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

- Growth
- Reproduction
- Immune response
- Maintenance

2 million years ago
CLIMATE CHANGE IN EAST AFRICA
↑ nutrient availability

Tradeoff: developing kidney energy consumption must be balanced with priority of energy allocation to brain

Homo habilis: Small brain, Big jaw

Homo sapiens: Big brain, Small jaw
Inter-organ competition for available energy

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

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

Pregnancy & breastfeeding $\rightarrow$ 20% $\uparrow$ 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


Govaert Bidloo. 1690
Epigenetics: intergenerational inheritance

Mother - 1st generation (F0)
Fetus - 2nd generation (F1)
Reproductive cells - 3rd generation (F2)

Barker. Placenta 33 Suppl 2:e30-4, 2012
EPIGENETICS: DNA methyltransferase1 activity Determinant of nephron number in mouse kidney

![Graph showing DNA methylation levels in control and restricted conditions.](image)

- Control vs Restricted: p=0.0430

![Graph showing estimated number of total progenitor cells.](image)

- E15.5 vs E19.5:
  - HET: Est. number of total progenitor cells
  - KO: Est. number of total progenitor cells

- p=0.00015

![Graph showing number of glomeruli.](image)

- WT vs KO:
  - E14.5: p=0.031
  - E15.5: p=0.040

- E19.5: p=0.030

Wanner JASN 30:63, 2019
Metabolic reprogramming $\rightarrow$ developmental plasticity

Glycolysis $\leftrightarrow$ OXPHOS

AMPK, mTOR

OXPHOS $\rightarrow$ 10x ATP/glucose vs glycolysis

Glycolysis $\rightarrow$ rapid energy availability

AMP-activated protein kinase mechanistic target of rapamycin
Oxygen and nutrient availability determine fetal nephron number through counterbalancing mechanisms.

**ENERGY CONSERVATION**

- **Hypoxia**
- **Malnutrition**

  \[ \uparrow \text{AMP/ATP} \]

  \[ \uparrow \text{AMPK activity} \]

  \[ \downarrow \text{nephrons} \]

  AMP-activated protein kinase

  **Autophagy mitophagy**

**ENERGY CONSUMPTION**

- **↑Amino acids**
- **↑Growth factors**
- **↑Retinol**

  \[ \uparrow \text{OXPHOS} \]

  \[ \uparrow \text{HIF} \]

  \[ \uparrow \text{Glycolysis} \]

  \[ \downarrow \text{HIF} \]

- **↑nephrons**

**Progenitor cell renewal**

- **↑O_2**
- **↓O_2**

- **Wnt/β catenin differentiation**

- **Nephron progenitor cell maturation**

- **Dnmt1**

  \[ \uparrow \] DNA methyltransferase1

  \[ \downarrow \text{nephrons} \]

  **Hypoxia inducible factor**

  Master regulator of mitochondrial biogenesis

Metabolic reprogramming determines renal progenitor cell fate
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.
Homo sapiens: Dispersion of mitochondrial haplogroups over 70,000 years

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

Cumulative risk of ESRD

Peak reproductive years

Posterior urethral valves
Solitary kidney
Bilateral hypodysplasia
Multicystic kidney

Adapted from Sanna-Cherchi. Kidney Int 2009
Future research on nephrogenesis: Focus on metabolism and epigenetic signaling

Progenitor Cell

Differentiating Cells

↓O₂

↑O₂

Epigenetic signaling

Metabolic reprogramming
The Future: In vivo measurement of nephron number

Cationic ferritin - enhanced magnetic resonance imaging
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.

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

Robert L. Chevalier
RLC2M@virginia.edu


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