Impact of Advanced Maternal Age (AMA) on Renal Development and Adult Outcomes in Offspring: A Mouse Model Study

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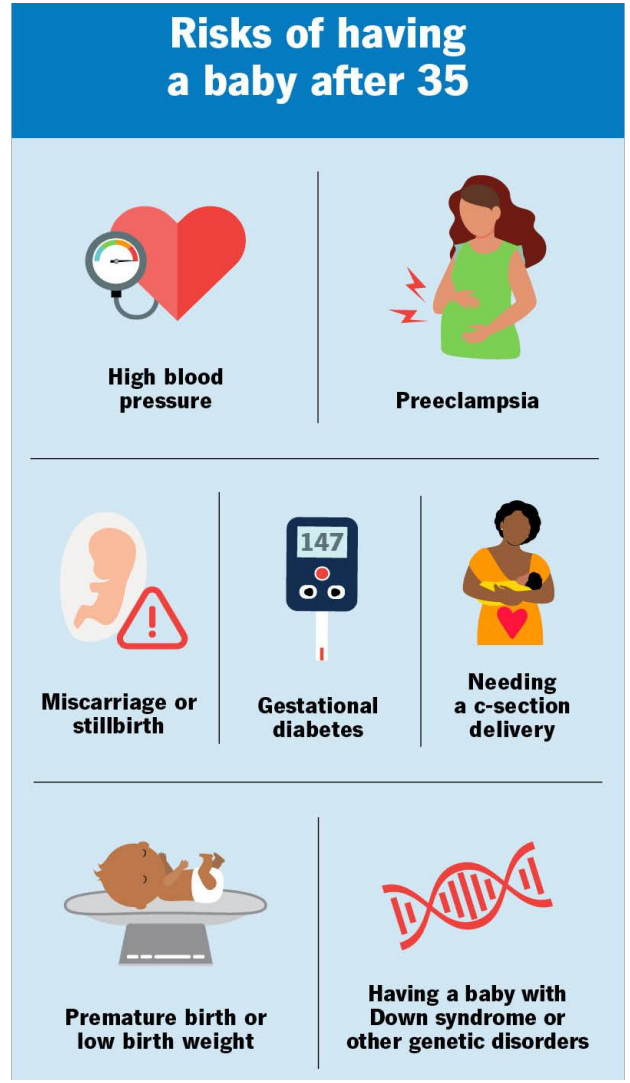
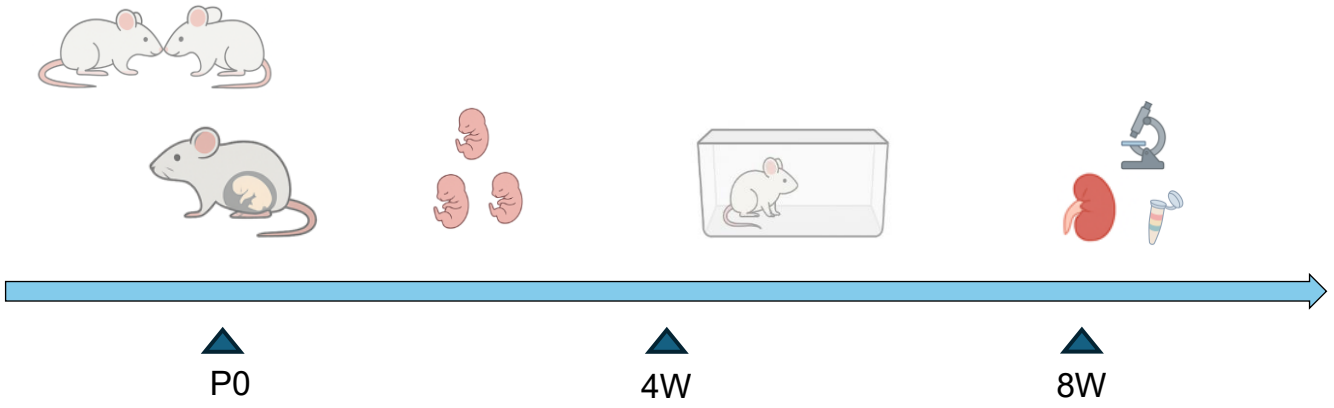
【Background and Purpose】

- **AMA (≥35 years) pregnancies** are increasing worldwide
- AMA are linked to more **low birth weight (LBW)** infants
- In DOHaD, **LBW + reduced nephron number → HT & CKD**
- Mechanisms, including **postnatal renal maturation**, remain unclear
- **Aim:** use an AMA mouse model to study **renal development and postnatal phenotypes**



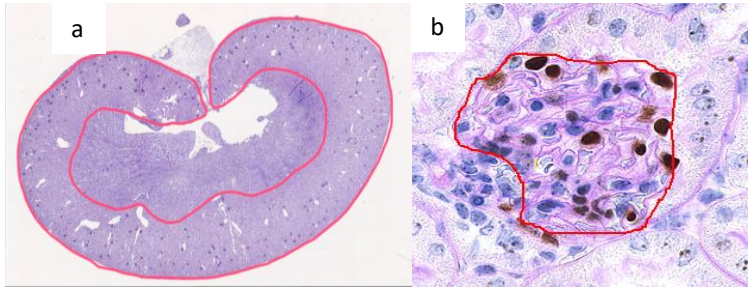
【Methods】



Mice: **Outbred Jcl:ICR**
Dams: **AMA ≥6 months** vs. CON 10–12 weeks
Sires: 10–12 weeks
Offspring: males only

- **P0:** BW, KW, qPCR (renal genes)
- **4W**: BW
- **8W**: BW, KW, BP (tail-cuff), U-protein, U-8-OHdG, histology, RNA-seq, metabolomics

Histopathology：PAS+WT1 immunostaining for Cortical glomerular density and Glomerular tuft area

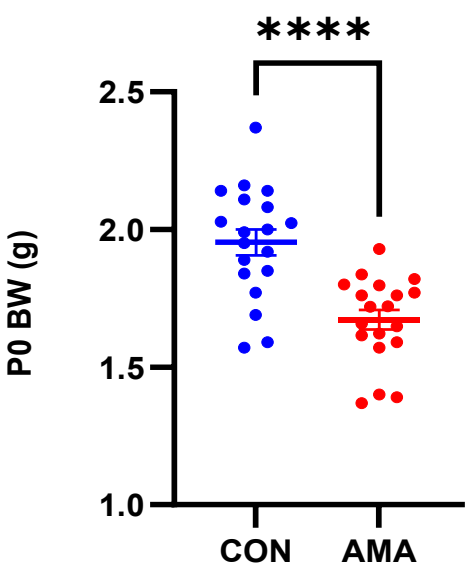


- **Cortical glomerular density**: glomeruli per cortical area
- **Glomerular tuft area**: tuft area including vascular pole

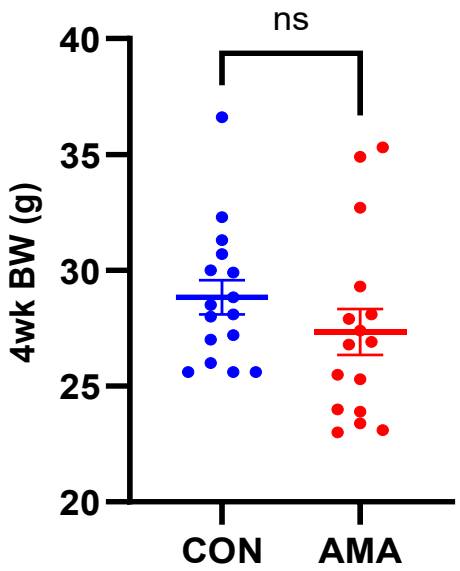
→to evaluate the Nephron number and glomerular hypertrophy in adult offspring.

【Results】 1. Body weight and blood pressure

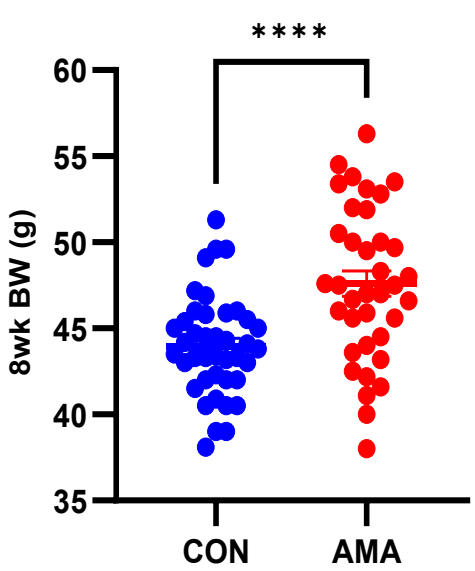
P0 BW



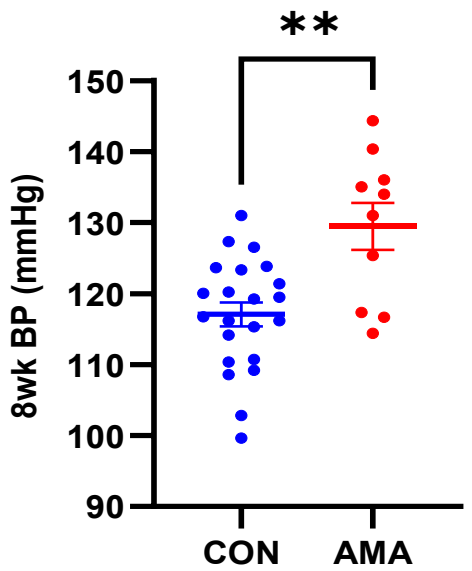
4wk BW



8wkBW



8wk BP



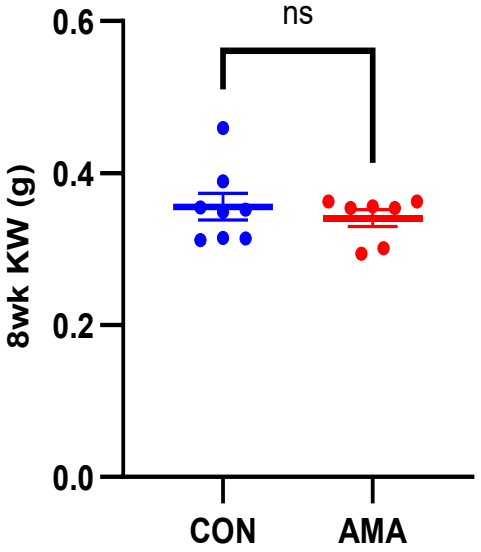
- BW

  P0: **AMA ↓ (LBW)** 4W: no difference (indicating catch-up) 8W: **AMA ↑**

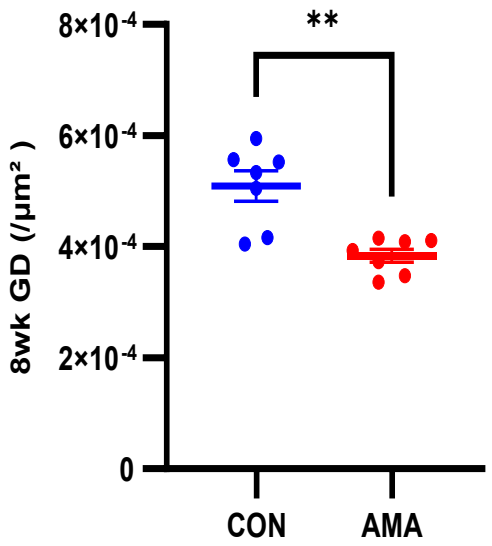
- BP (8W): **AMA ↑**

【Results】 2. Renal morphology and urinary protein level (8W)

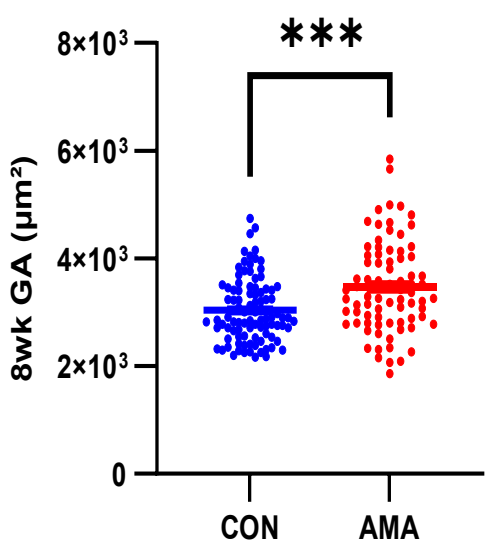
Kidney weight



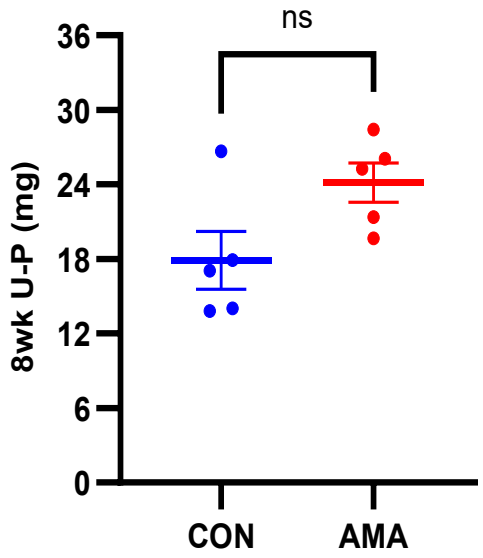
GD



GA



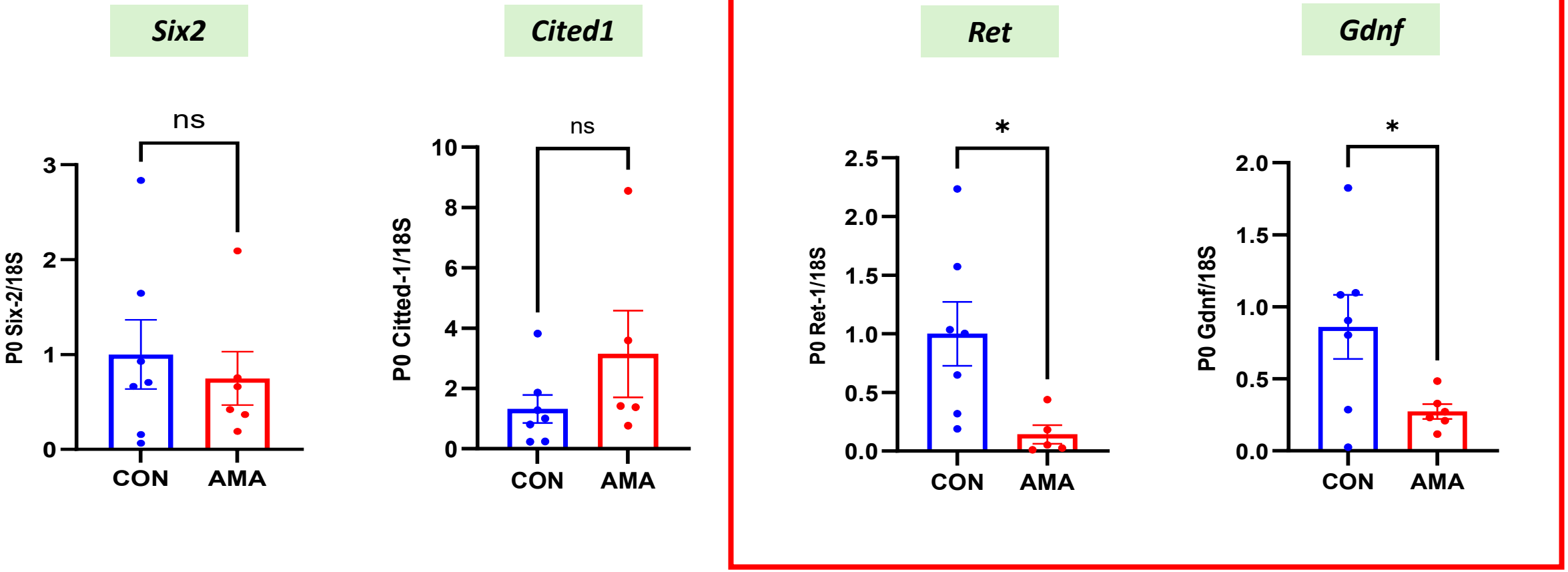
U-P



- Kidney weight: similar
- **Glomerular density: AMA ↓**
- **Glomerular tuft area: AMA ↑**
- **Urinary protein: trend ↑ in AMA**

→suggesting glomerular hyperfiltration

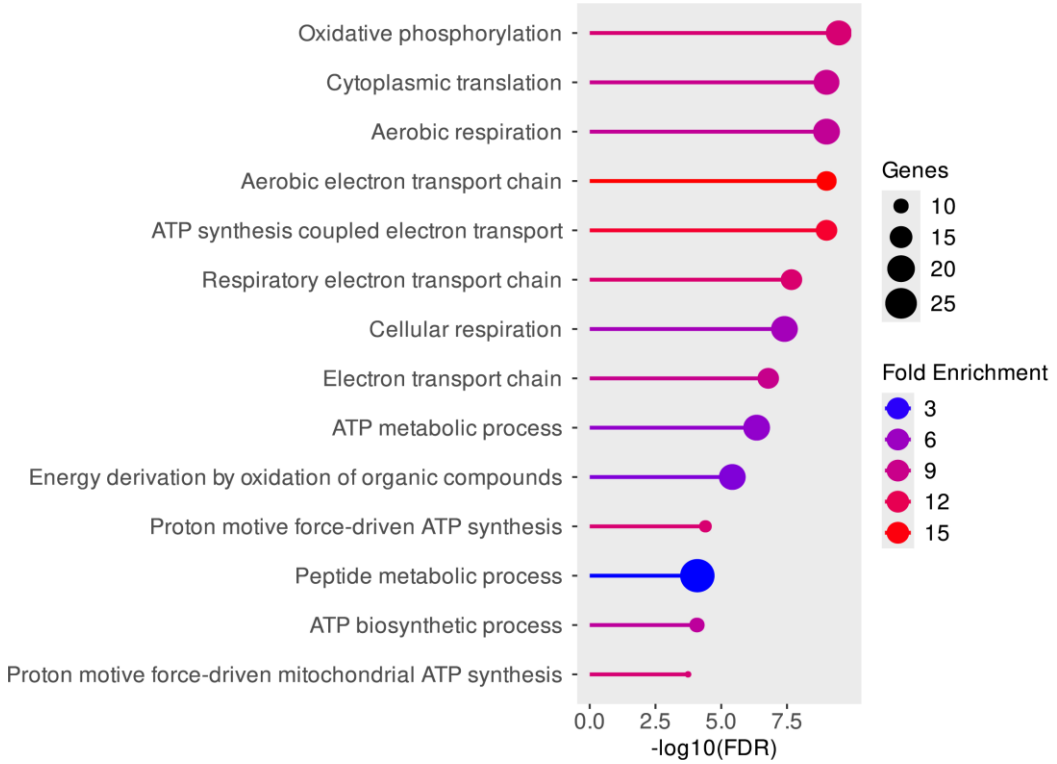
【Results】 3. Gene expression at P0

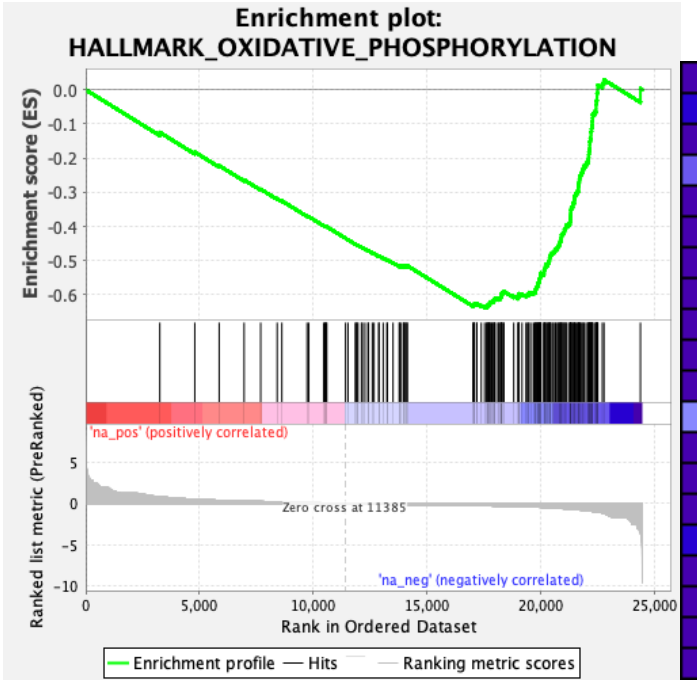


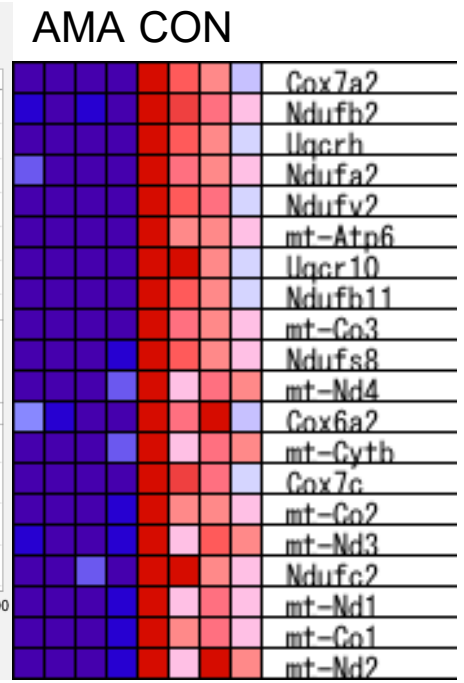
- Mesenchyme markers (*Six2, Cited1*): no difference
- **Ureteric bud markers (*Ret, Gdnf*): AMA ↓**

→indicating suppression of UB branching

【Results】 4. Bulk (whole kidney) RNA-seq (8W)







- GO genes enriched in: **oxidative phosphorylation, aerobic respiration, electron transport chain, ATP metabolic process**
- GSEA: OXIDATIVE_PHOSPHORYLATION pathway: **down-regulation in AMA**
- Many mitochondrial genes: **lower in AMA**

【Results】 5. Mitochondrial content and oxidative stress markers

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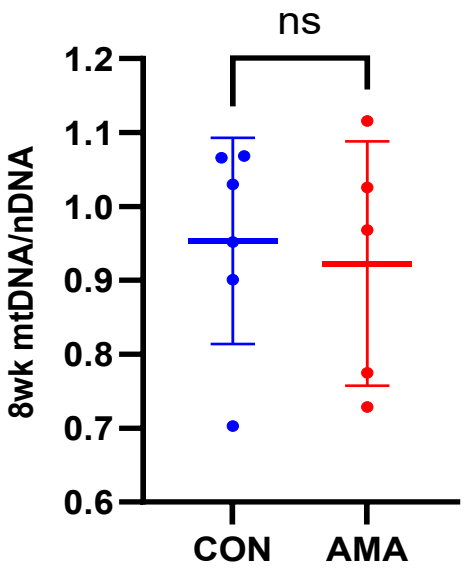
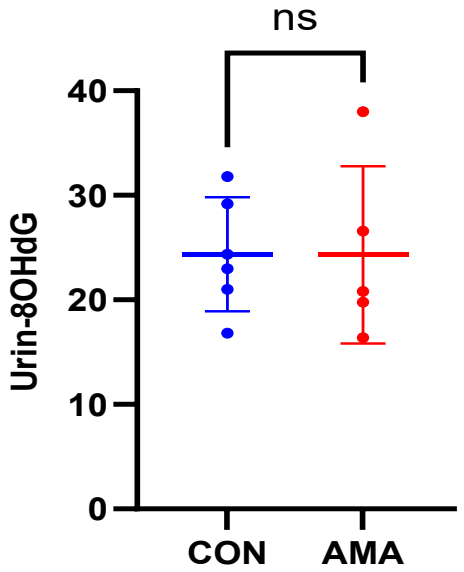
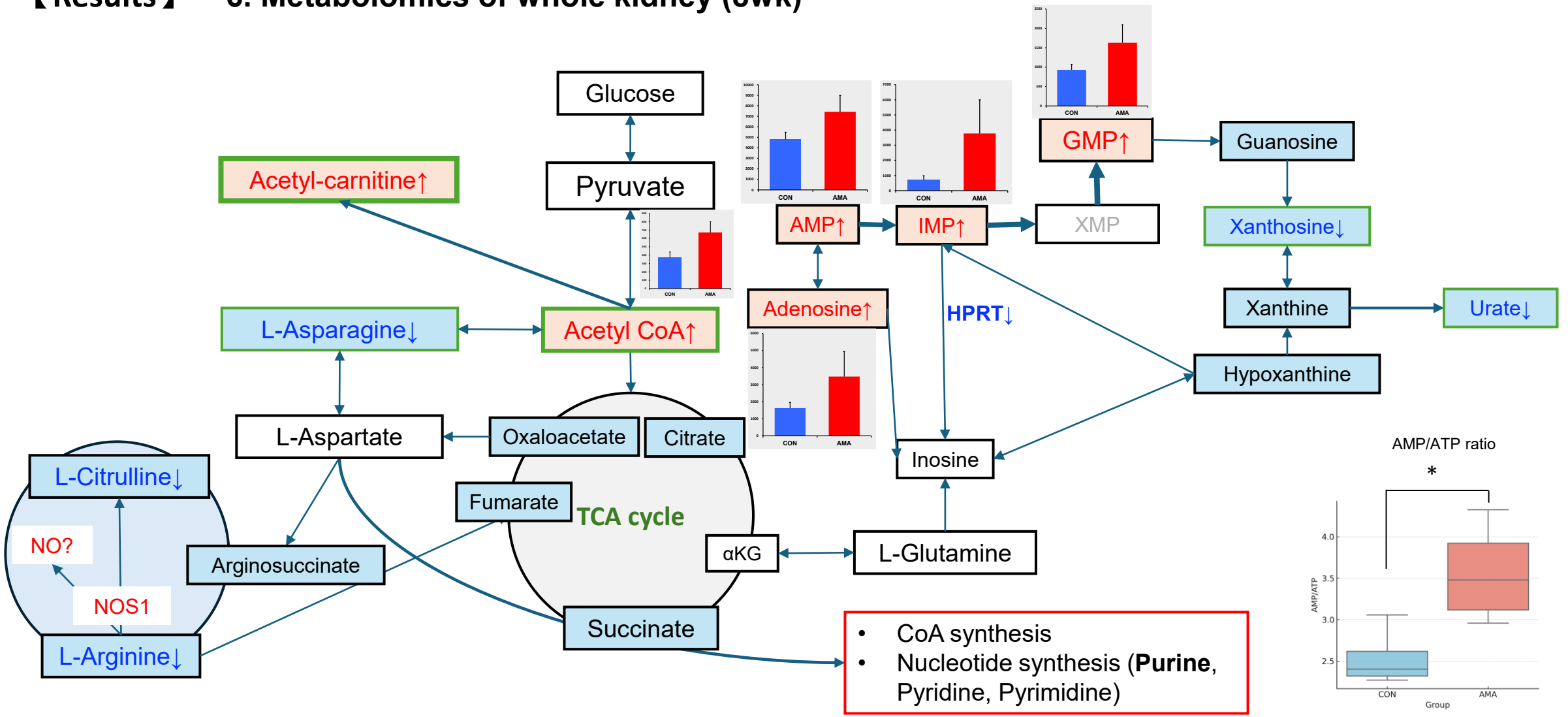


8OHdG



- mtDNA copy number (8W): similar
- Urinary 8-OHdG: similar

【Results】 6. Metabolomics of whole kidney (8wk)



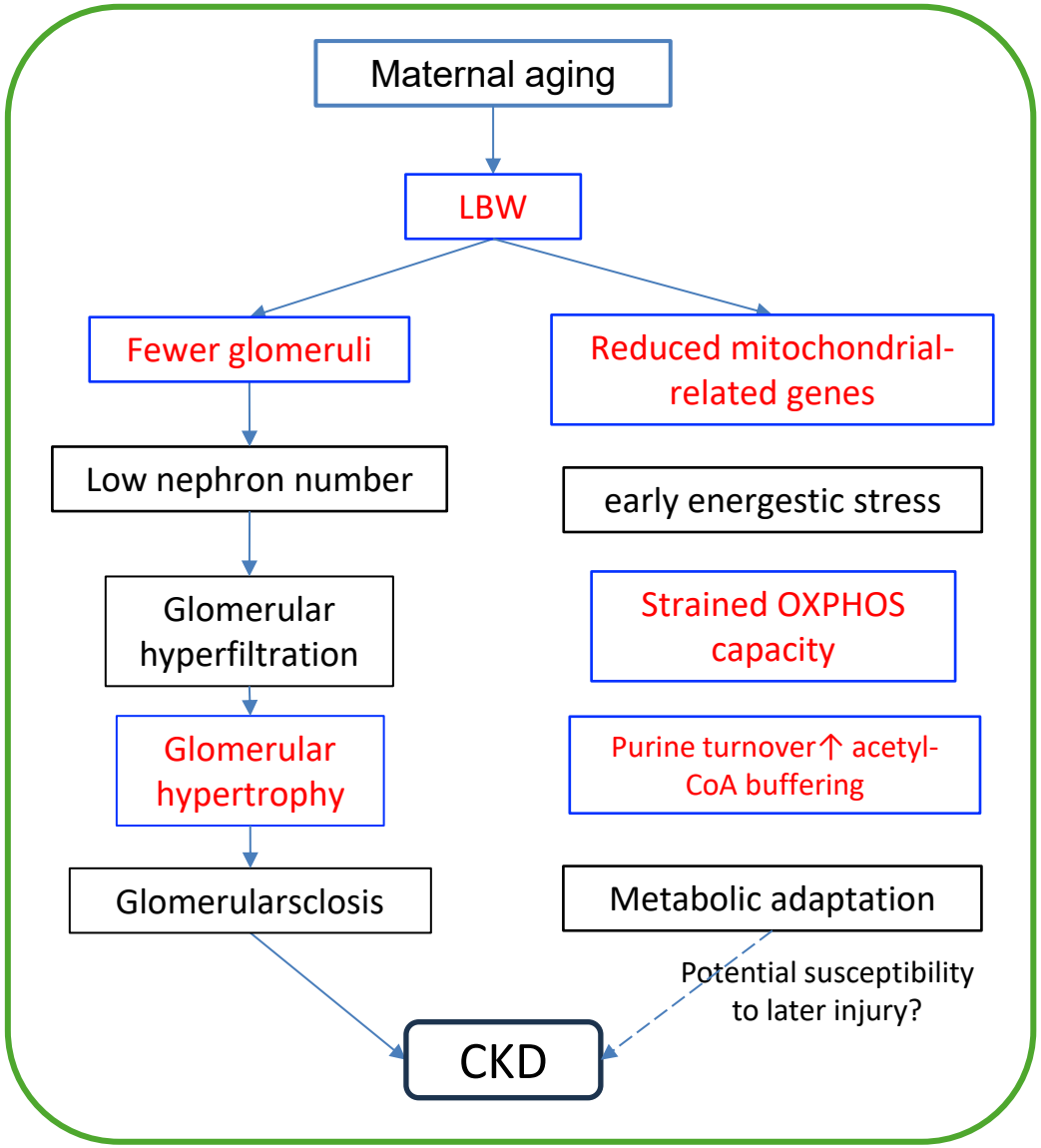
Elevation ↑ Acetyl-CoA, O-acetylcarnitine

However, TCA intermediates: mild reduction but no significance

On the other hand, AMA ↑AMP, IMP, and GMP ↓Xanthosine, Urate

→the elevation of purine turnover

【Disccussion】



AMA offspring:

LBW, catch-up growth, ↑BP

↓ nephron number, glomerular hypertrophy

→**suggestion of DOHaD frameworks**

Molecular level of Kidneys:

↓ reduction of Mitochondrial gene expression

↑ accumulation of acetyl-CoA / O-acetylcarnitine

↑ enhanced purine turnover

→**These findings may act as a DOHaD-related factor increasing the risk of CKD in later life.**

【Conclusion】

AMA mouse offspring show:

- LBW and postnatal catch-up growth
- Fewer nephrons and glomerular hypertrophy
- Higher BP in early adulthood

Kidneys exhibit:

- Metabolic / mitochondrial adaptations
- Enhanced purine-related energy handling
- Limited metabolic reserve → vulnerability to future renal stress

COI
All authors declare no conflicts of interest related to this presentation.