Nicotinamide Adenine Dinucleotide deficiency and birth defects: where, when, and why?

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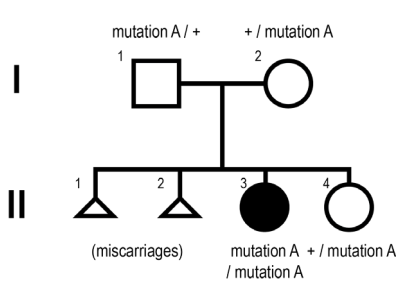
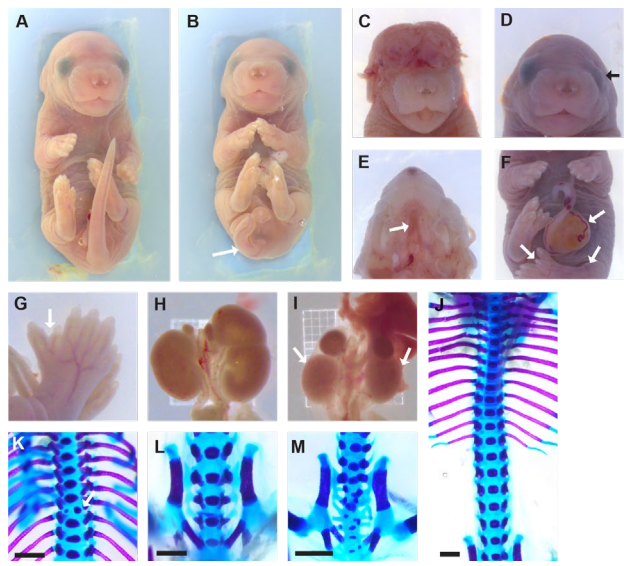
What is NAD?

- Nicotinamide Adenine Dinucleotide (NAD) is an essential cofactor involved in many biological processes including DNA repair, metabolism, circadian rhythm, immunity, injury and stress response, and epigenetics
- If NAD levels are too low, these processes are likely to be affected

Loss of *KYNU, HAAO*, or *NADSYN1* causes birth defects

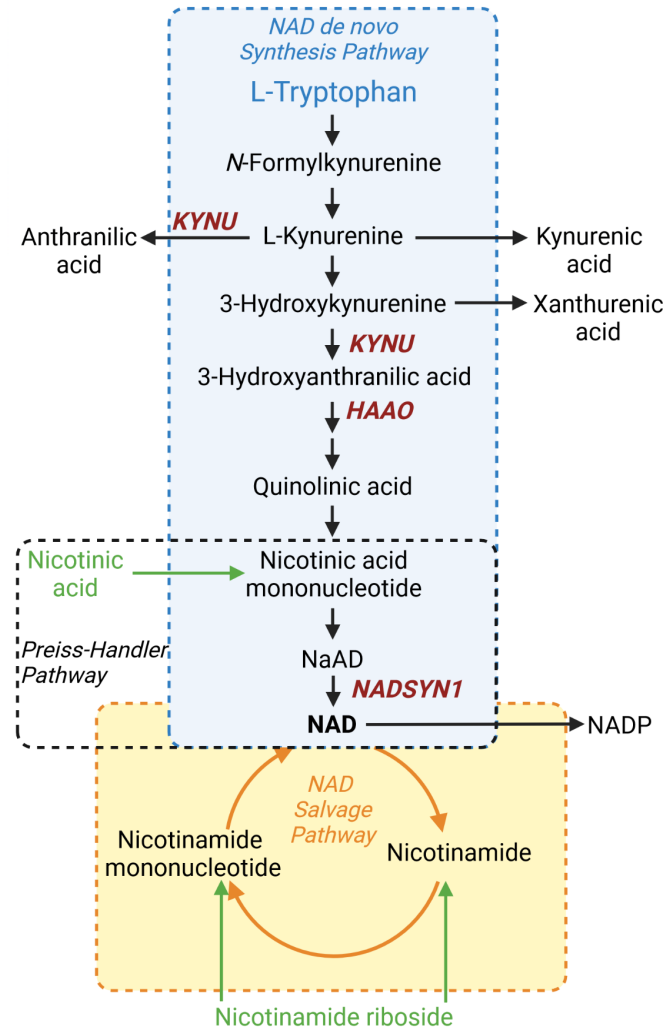
- Biallelic mutation of these genes in humans causes malformation of the **vertebrae**, **heart**, **kidneys**, and **limbs**
- We can reproduce these defects in mouse embryos when these genes are knocked out





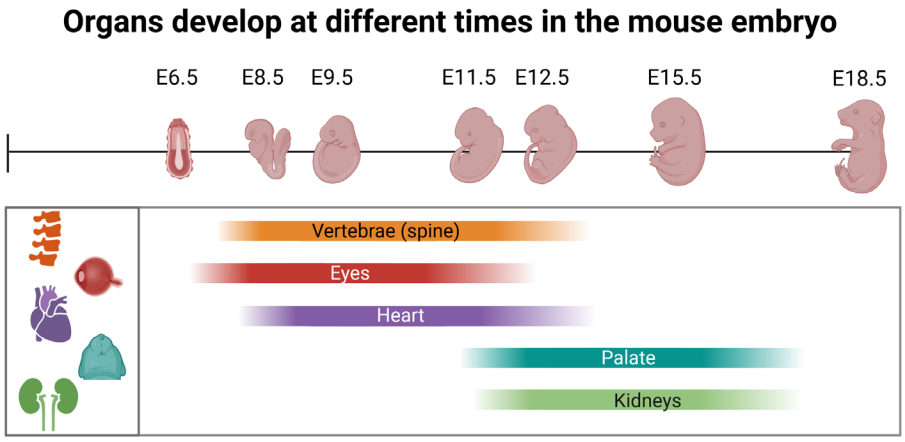
(above) Pedigree showing inheritance of disease-causal gene mutations; **(right)** Malformations observed in mouse embryos lacking functional NAD biosynthesis genes

How is NAD made?



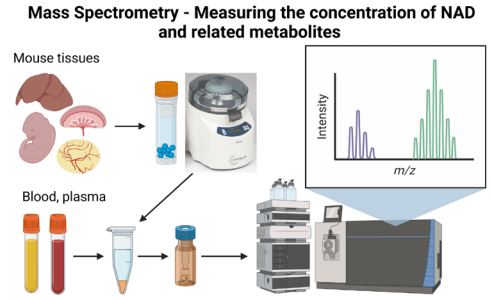
(above) NAD is synthesised from dietary precursors. Mutations of genes involved in ***de novo* NAD synthesis** (***KYNU, HAAO, NADSYN1***) prevents sufficient generation of NAD and causes malformations in humans and mice

What are we trying to understand?

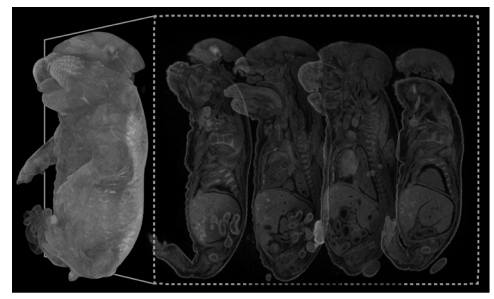


When does NAD deficiency occur and what organs are affected?
Why are specific organs affected?
Can this deficiency be prevented?

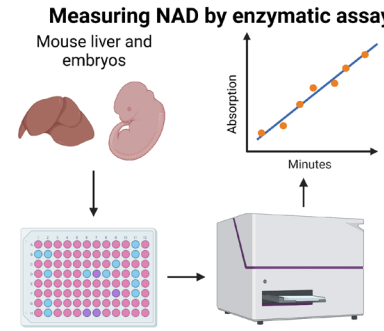
How can we study NAD deficiency?



(left) Computer-automated comparisons of observed defects to healthy reference embryo atlas



(above) Micro-CT cross-sectional examination of scanned embryos



Why join us?

Talk to us Wednesday 6th July 2022, 4 – 5:30 pm (Microsoft Teams meeting): **Click here to join the meeting**