* Title: Arginase I deficient mice exhibit decreased myelination, \*degraded\* endothelial tissue, and a distinct transcriptomic signature
* Authors
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* Abstract/Summary
  + Arginase I (ArgI) deficiency in humans is associated with several neurological impairments, such as spasticity, seizures, and intellectual disability. The source of these neurological problems is poorly understood. In order to better understand the neurological pathology of ArgI deficiency, we investigated the prefrontal cortex transcriptomes of P13, P14, and P15 ArgI knock-out, heterozygous, and treated knock-out (AAV-based gene therapy given on day 2 of life) mice using microarray technology. Weighted Gene Co-Expression Network Analysis (WGCNA) of our gene expression data revealed several dysregulated gene modules in the knock-out mice and highlighted trends in gene expression across genotypes. Genes involved in myelination were down-regulated in the knock-out, and genes representative of endothelial cells in the brain were also down-regulated in both the knock-out and treated knock-out. \*Subsequent histology interrogation of the knock-out mice revealed depletion of both myelin and endothelial tissue.\* Many genes involved in cellular regulation and response to toxicity were also dysregulated in the knock-out mice. Additionally, gene expression in each dysregulated gene module had an ArgI dose-dependent trend independent of concurrently collected blood arginine and ammonia concentrations. These results taken together implicate decreased myelination, degraded endothelial tissue, and a distinct transcriptomic signature as key components of the neurological manifestation of ArgI deficiency.
* Introduction/Background
  + Arginase I definition, function, and established role
  + Arginase I deficiency in humans
    - Figure 1
  + Previous research findings about Arginase I in the brain
  + Utilization of the transcriptome to understand the pathology of Arg1 deficiency
* Results
  + Mice, phenotypes, and microarray (brief pre-processing)
  + ArgI transcript/protein expression in mice
    - Figure 2
      * Western Blots, barplot of transcript
        + Add error bars, make it the mean
  + Other Top Differentially expressed genes
  + WGCNA
  + Dysregulated modules (via ANOVA)
    - Figure 3
      * Each dysregulated module, hub gene net, ANOVA bars
    - GO term enrichment
    - pSI cell type enrichment
    - BBB gene enrichment
    - Diff Expr. Gene enrichment
    - PPI enrichment
  + Histology of Mice
    - What do we find?
    - Figure 4
      * Pictures of degradation?
  + Transcriptomic ArgI Dose-Dependent Trend
    - ArgI deficiency has noticeable effect on the transcriptome regardless of current ammonia and arginine concentrations
      * Byproduct of arginine?
      * Lack of ArgI?
      * Excess ammonia and arginine acting earlier in development and leaving an effect?
      * Transcriptomic dysregulation NOT due to current concentrations of ammonia and arginine
    - Figure 5
      * ME plot of dysregulated modules
      * Barplot of ammonia and arginine levels
* Conclusions/Discussion
  + Dysregulation of myelination and endothelial tissue
  + General RNA processing, cellular regulation, and response to toxicity abnormalities in gene expression
  + Transcriptomic signature associated with ArgI deficiency
  + Future Directions
    - Conditional knock-out to hone in on if neurological deficits we see are due to
      * Lack of ArgI in the brain
      * Excess arginine/ammonia and/or byproduct detrimentally effecting the brain
      * Will be robust to time of effect (pre or post natal)