

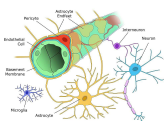
NOTCH3 DEFICIENCY ACCELERATES THE NEUROVASCULAR AGING CLOCK VIA INNATE IMMUNE ACTIVATION AND VASCULAR SMOOTH MUSCLE CELL SENESCENCE

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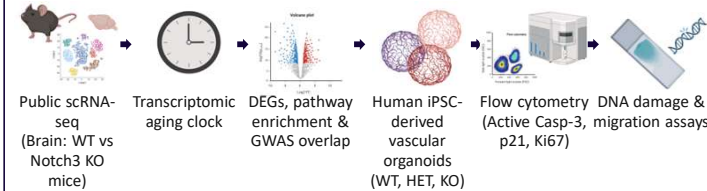
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BACKGROUND

- Neurovascular unit (NVU) dysfunction is a hallmark of early Alzheimer's disease (AD).
- NOTCH3 mutations cause CADASIL, but its role in broader neurovascular aging is not well understood.
- We investigated how NOTCH3 loss impacts the biological aging trajectory and functional survival of brain vascular smooth muscle cells (vSMCs).



METHODS



Integrated transcriptomic and functional analyses reveal how NOTCH3 deficiency drives neurovascular aging and vulnerability.

KEY FINDINGS

- NOTCH3 loss accelerates the biological age of vSMCs and astrocytes based on transcriptomic aging clocks.
- NOTCH3-deficient human vascular organoids show increased DNA damage, senescence (p21), apoptosis (active Caspase-3), and impaired migration.
- DEGs in Notch3 KO vSMCs are enriched for AD-associated GWAS traits, including Alzheimer's disease, cognitive performance, memory performance, and brain volume.

FIGURE 1. Transcriptomic aging clock in brain cells

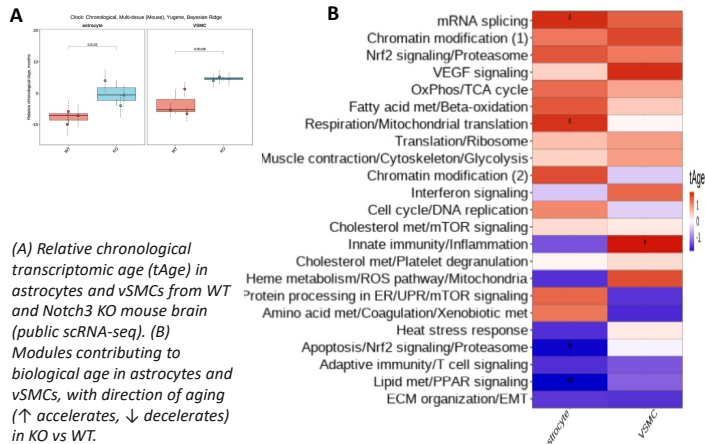


FIGURE 2. Cellular phenotyping in human iPSC-derived vascular organoids

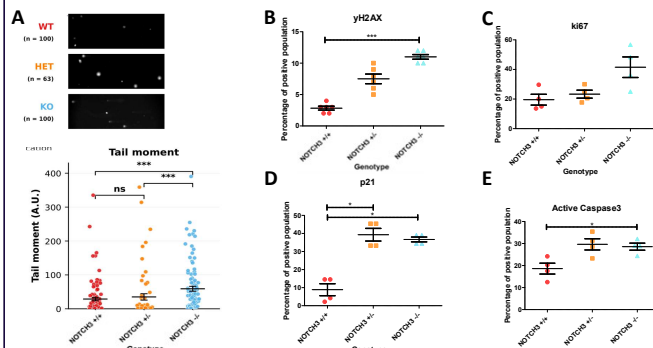


FIGURE 3. Functional validation in human iPSC-derived vascular organoids

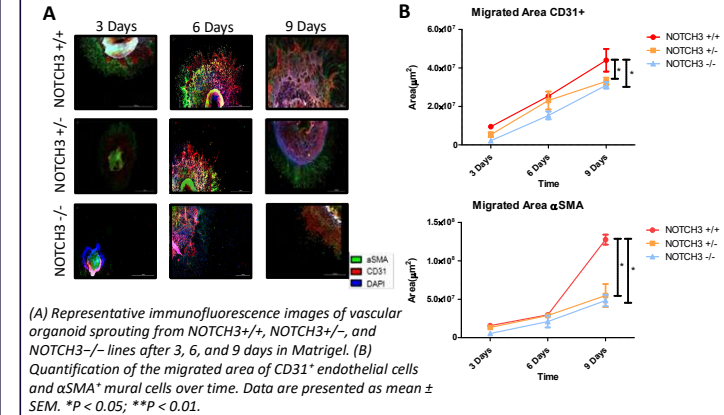
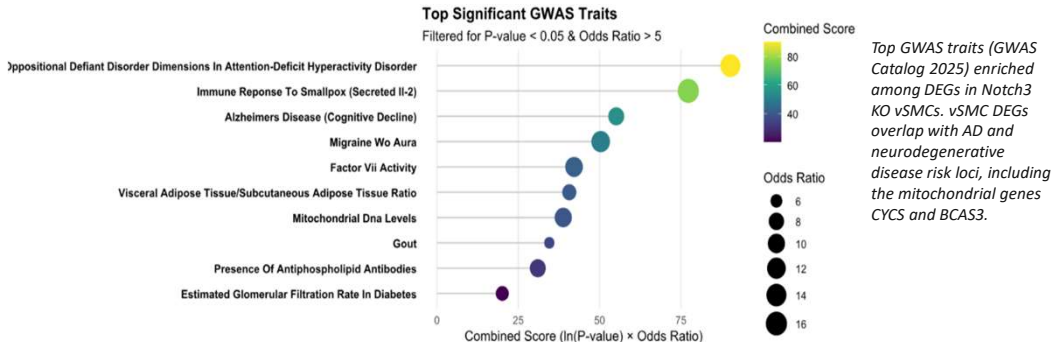
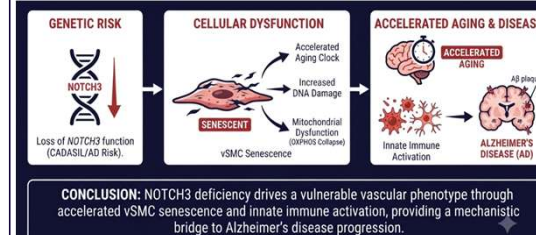


FIGURE 3. GWAS Catalog enrichment of DEGs in Notch3 KO vSMCs



CONCLUSIONS



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