

A Comprehensive Genome-wide Association Analysis Of Hirano Body Pathology Across Neurodegenerative Brain Diseases

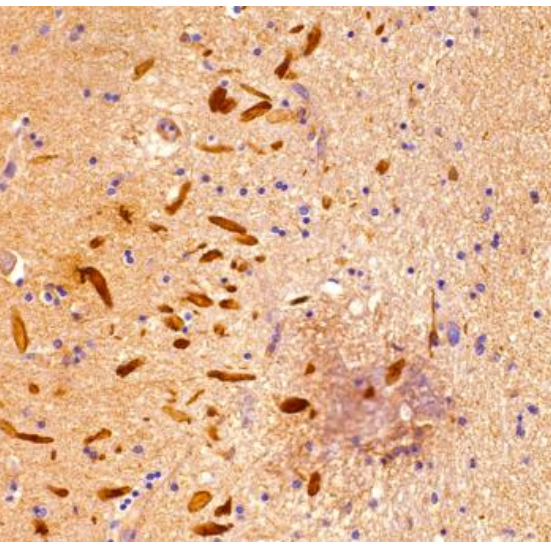
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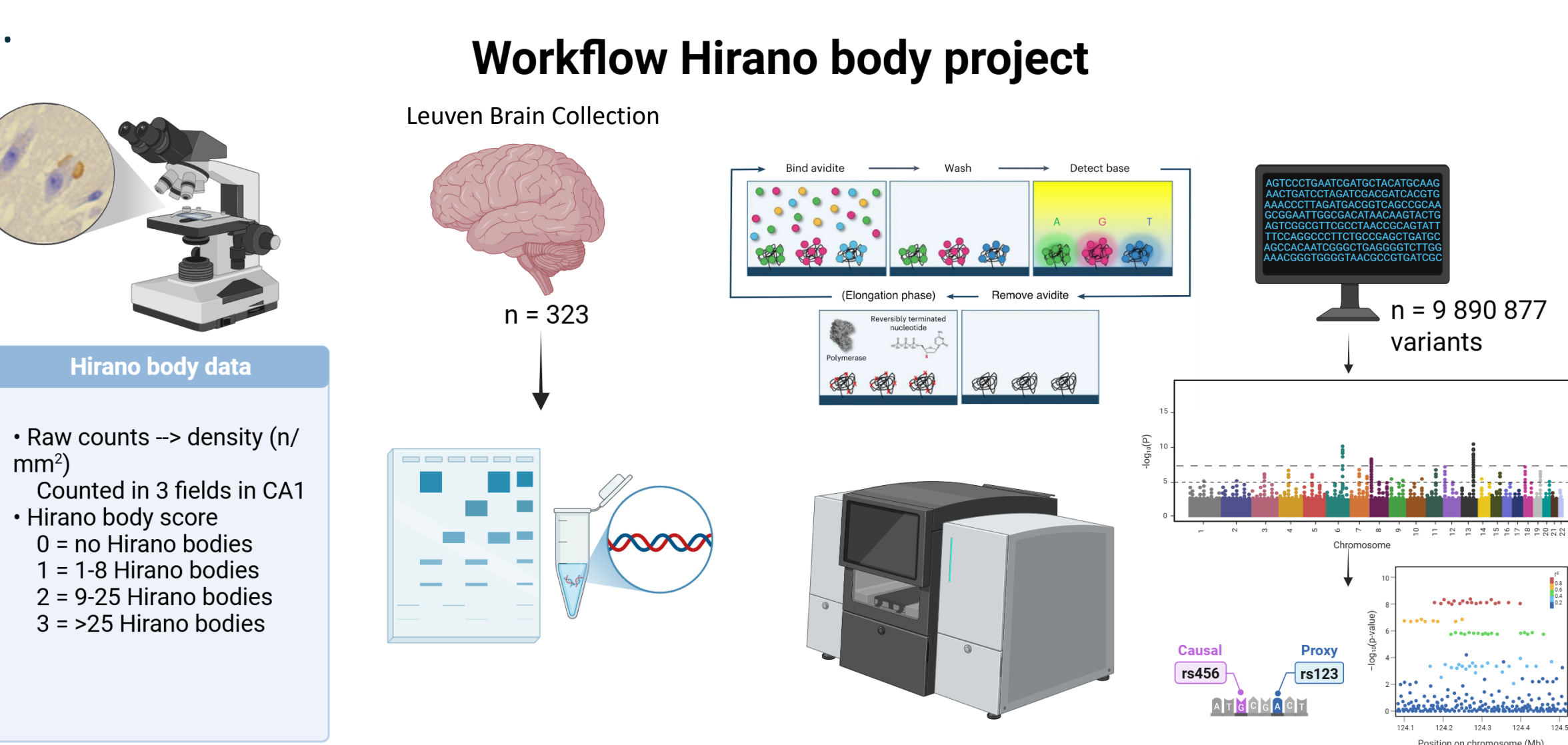
INTRODUCTION

The classical **hallmarks of Alzheimer's disease (AD)** are extracellular **A   plaques** and intracellular **tau tangles**. However, in the vast majority of AD patients, **co-pathologies** are observed which can influence the disease profile. One such co-occurring feature is **Hirano body (HB) pathology**. They are commonly observed in neurodegenerative brain diseases but vastly understudied. HBs are crystalline **actin** aggregates found mainly in the neuronal cytoplasm in the **CA1** region. Besides actin, tau and AICD fragments are observed. Three morphological shapes are observed: string, balloon and rod-shaped. The involvement of HBs in disease is largely unknown.

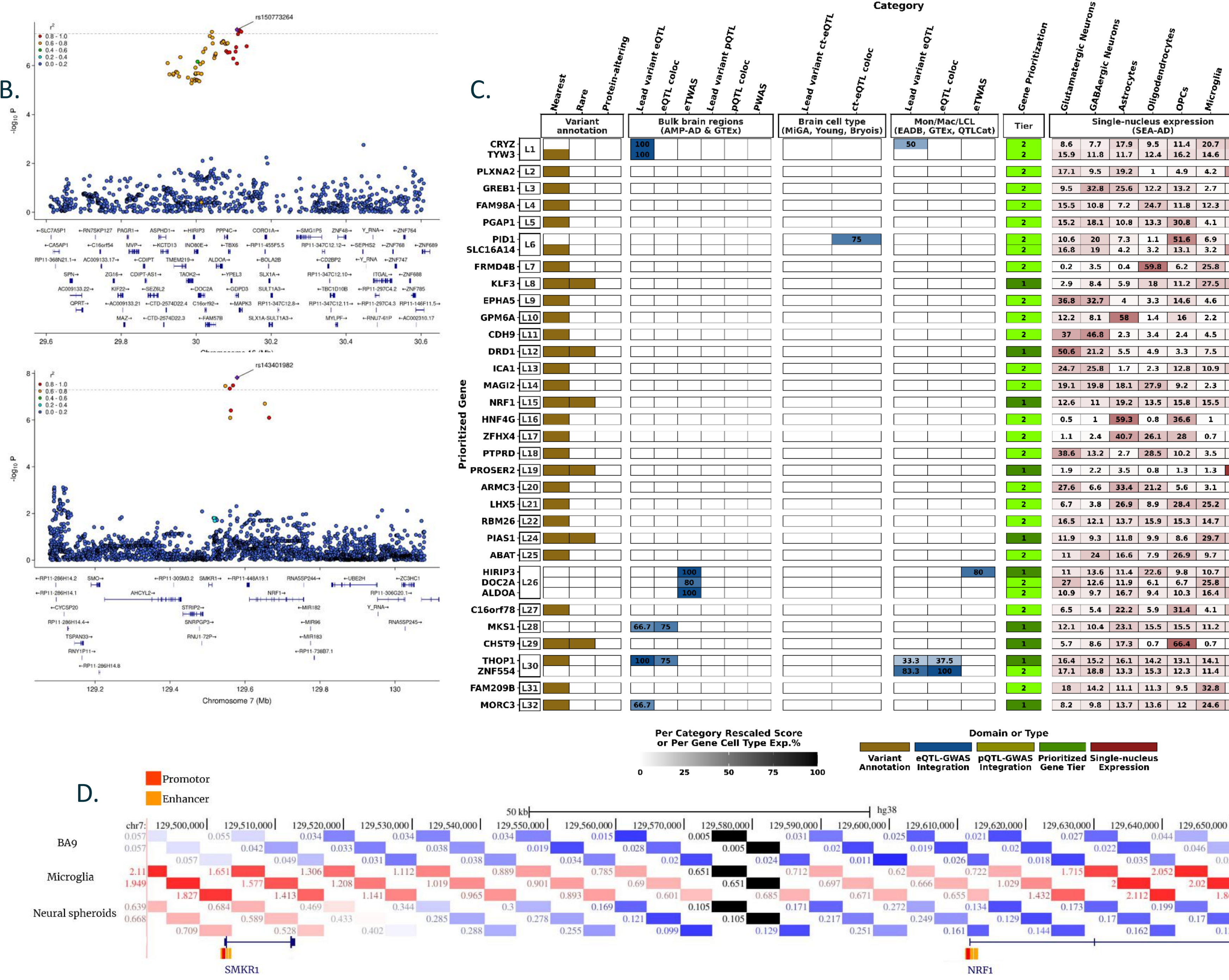
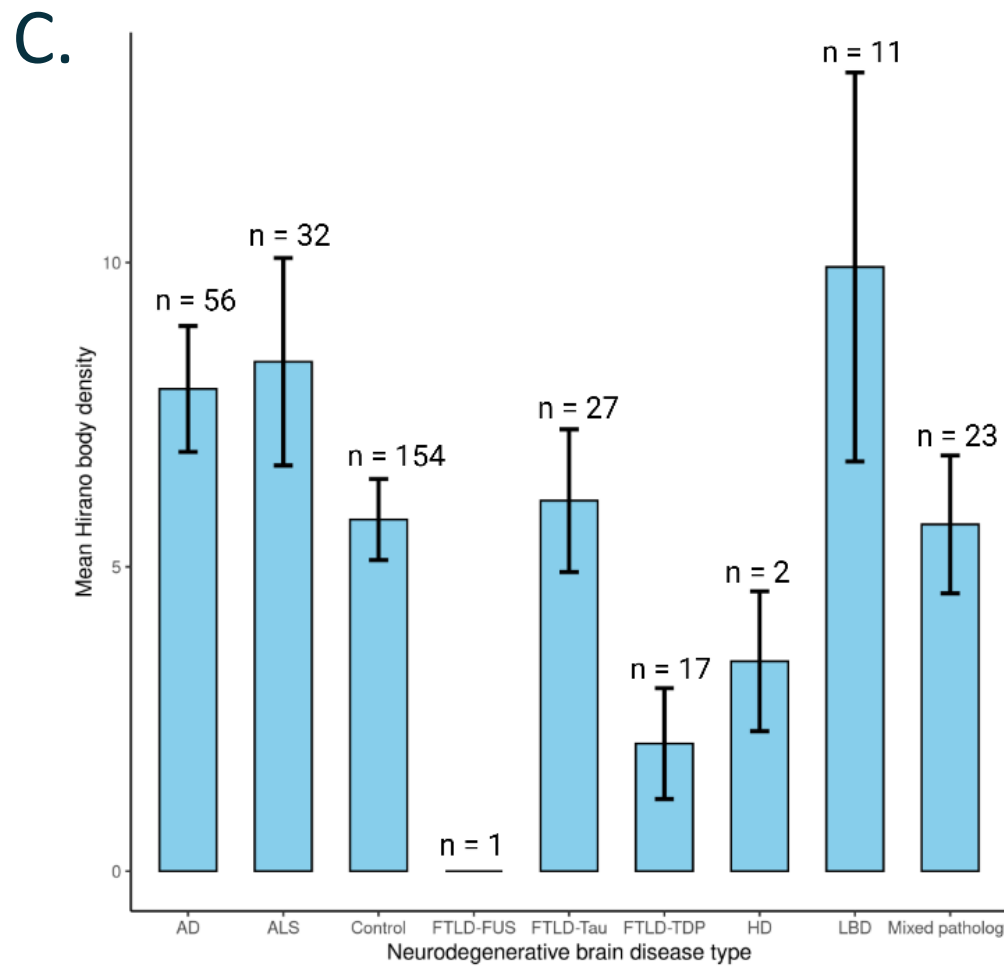
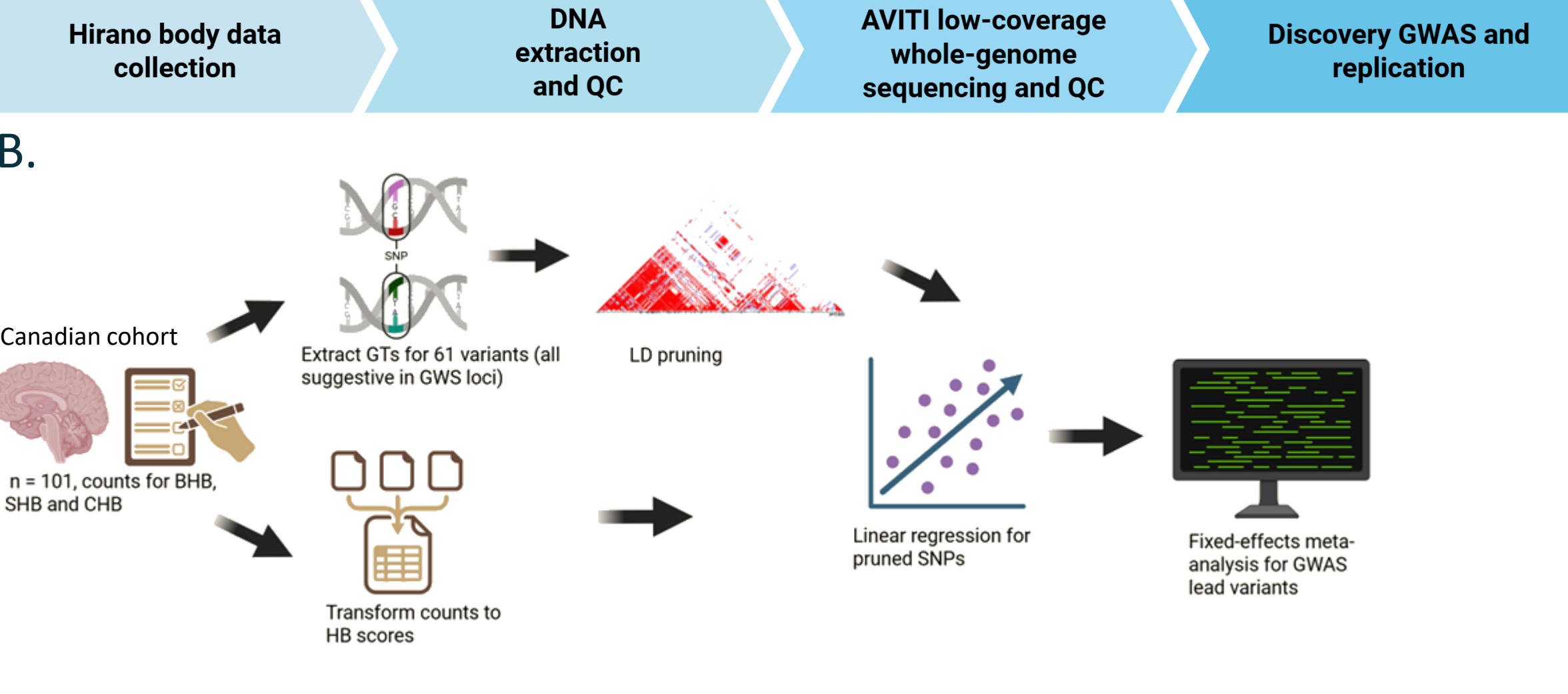


Goal: Use GWAS to gain insight into the etiology and functional mechanisms underlying Hirano body formation

METHODOLOGY AND HIRANO BODY COHORT



Panel 1. **A.** A schematic workflow of the HB project describing the semi-quantitative score used to represent HB pathology and the subsequent workflow used to generate WGS data. Low-coverage WGS data was imputed with GLIMPSE2 and used for GWAS. **B.** Overview of the replication analysis. Replication was done in an independent cohort for which HB counts were generated for each HB shape. Genome-wide significant variants from the discovery analysis were LD pruned per locus and tested for association in the replication cohort. **C.** A graph showing the average HB count over three microscopic fields for individuals with different neurodegenerative brain diseases in the discovery cohort (part of the Leuven Brain Collection).



Panel 2. **A.** Manhattan plot showing the result for the HB score discovery GWAS using a linear regression model. **B.** Regional plots for the two genome-wide significant loci with the nearest genes being *GDPD3* and *NRF1*. **C.** Results from a weighted gene prioritization pipeline for two genome-wide significant and 30 suggestive loci. Gene prioritization was based on variant annotation, eQTL/pQTL, TWAS/PWAS and colocalization analyses. A tier is assigned representing the plausibility of a prioritized gene being the true causal risk gene with tier 1 being higher than tier 2. **D.** For the *NRF1* locus, gene prioritization was supplemented by investigation of HiC data generated on human iPSC-derived cells, interrogating the interaction frequencies of a 5kb bait containing the intergenic GWAS lead variant with promotor/enhancer regions of the two nearest genes.

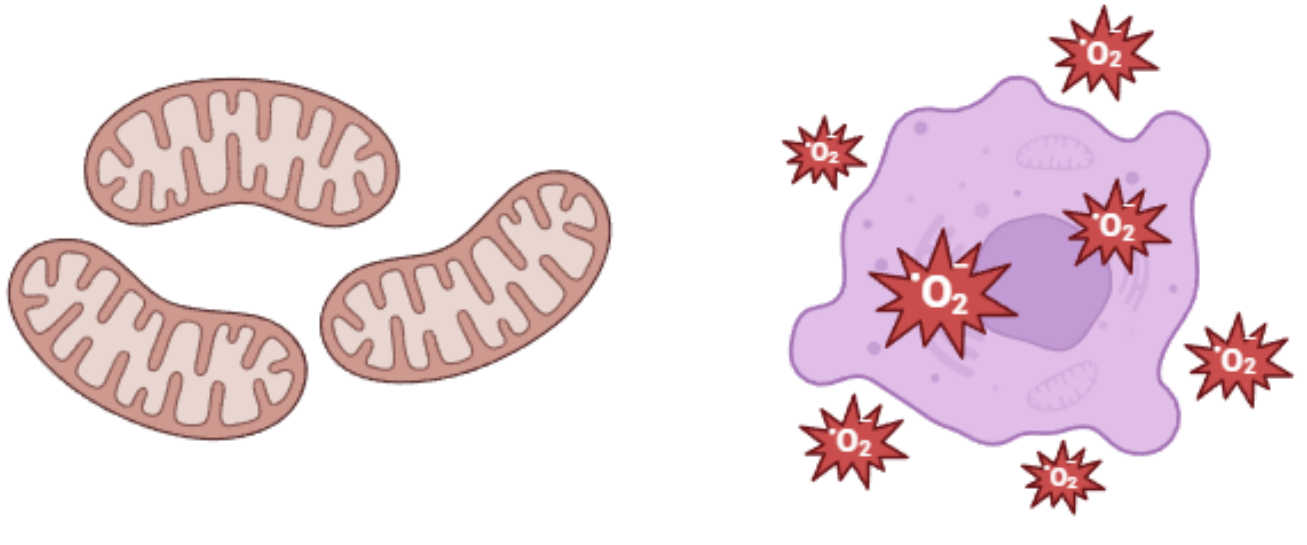
RESULTS



CONCLUSIONS AND FUTURE PERSPECTIVES

Two genome-wide significant loci from GWAS resulting in **six prioritized genes** associated with Hirano body score. Genome-wide significant loci were replicated in an independent cohort for balloon-shaped Hirano bodies.

<i>NRF1</i>	<i>SMKR1</i>	<i>GDPD3</i>
<i>ALDOA</i>	<i>DOC2A</i>	<i>HIRIP3</i>



Genes that were implicated are generally involved in **mitochondrial biogenesis** and processes related to **oxidative stress responses**, indicating that **Hirano body** formation might be a **general response to stress** in the neuronal environment. Their functional implication and the involvement of the proposed genes needs to be investigated further using **functional validation experiments**.