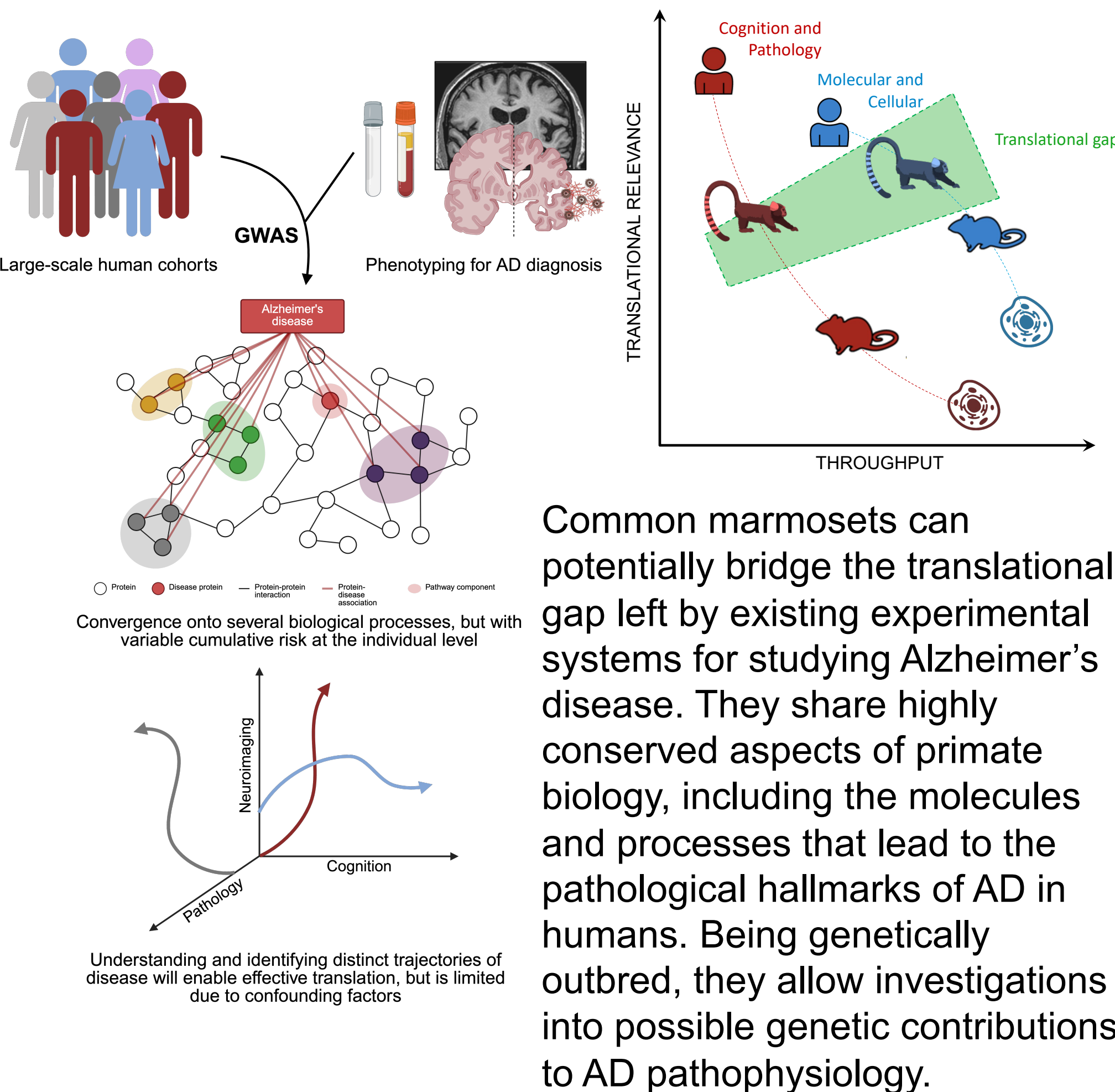


CNTN5 as a candidate locus driving plasma NfL variation in a population of laboratory marmosets

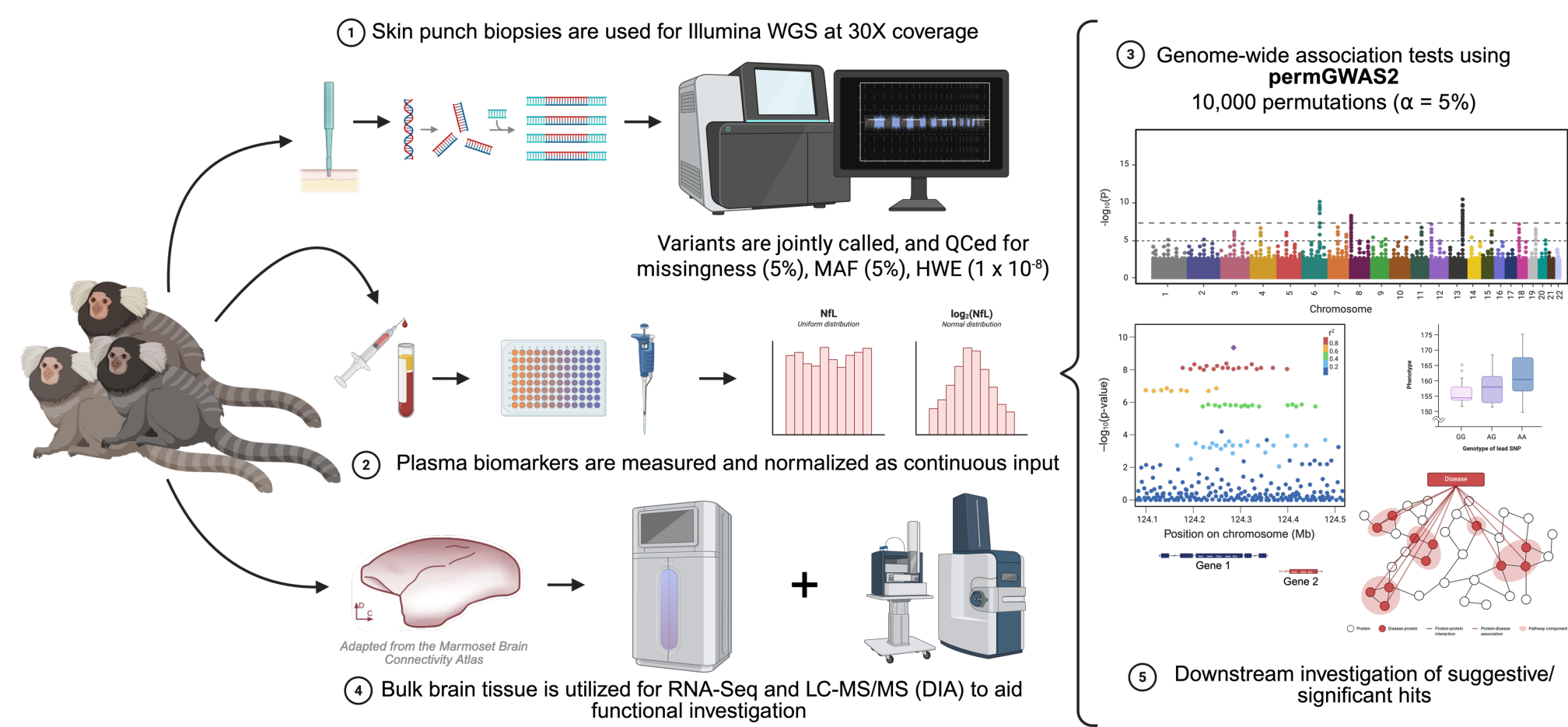
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INTRODUCTION



METHODS



1. Suggestive variant on chromosome 10 highlights the CNTN5 locus in association with plasma NfL levels

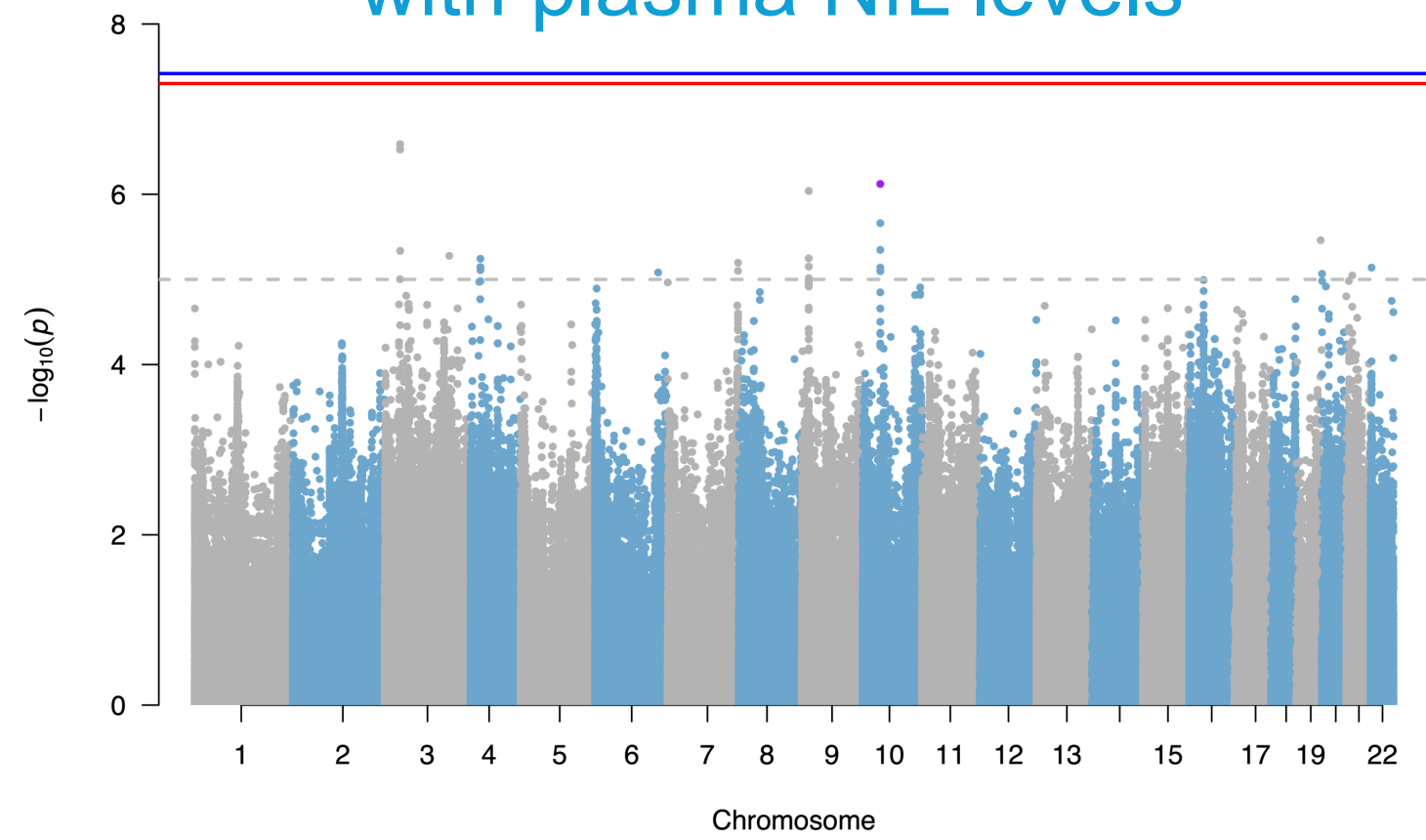


Fig. 1: Manhattan plot showing genome-wide associations with plasma NfL. Empirical p -value threshold calculated by permutation testing is shown in blue, with the standard $p < 5 \times 10^{-8}$ shown in red. Suggestive hits are those above the dashed grey line (10^{-5}). $N = 182$ marmosets, covariates used in the model included age and sex. ($p = 7.566 \times 10^{-7}$, effect size = -0.282, S.E. = 0.059).

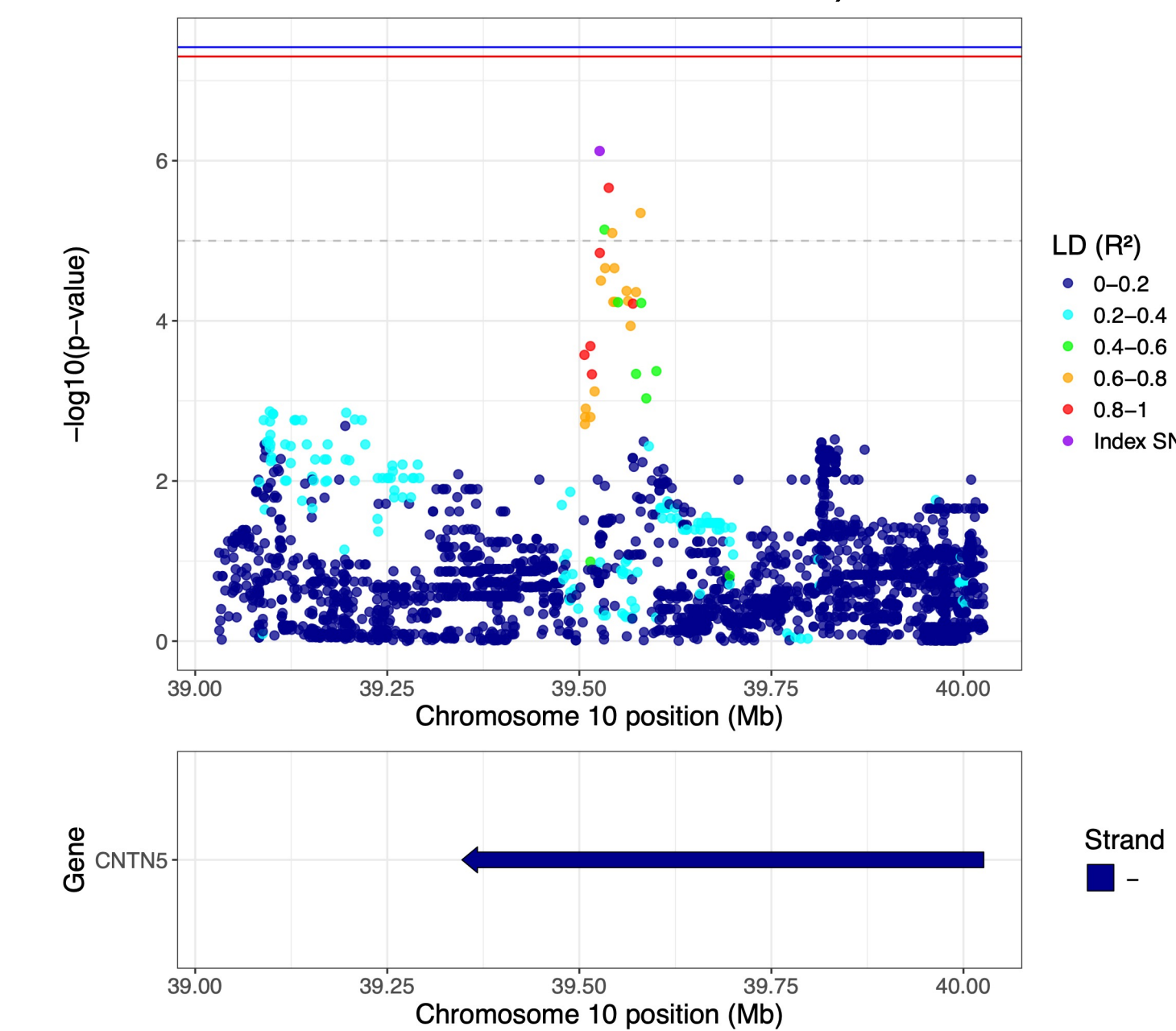


Fig. 2: The lead SNP is shown in purple, with LD indicated for related variants in the locus. The SNP of interest is in high LD with numerous SNPs, all occurring within the gene *CNTN5*.

RESULTS

2. SNPs in high LD at the CNTN5 locus are all non-coding in nature

Variant type	Variant impact	No. of variants
Intronic	Modifier	27

Variants in high LD (phased $R^2 \geq 0.5$ in Fig. 2) with lead SNP were shown to localize within the gene structure of *CNTN5*, with variant effects and impacts summarized here.

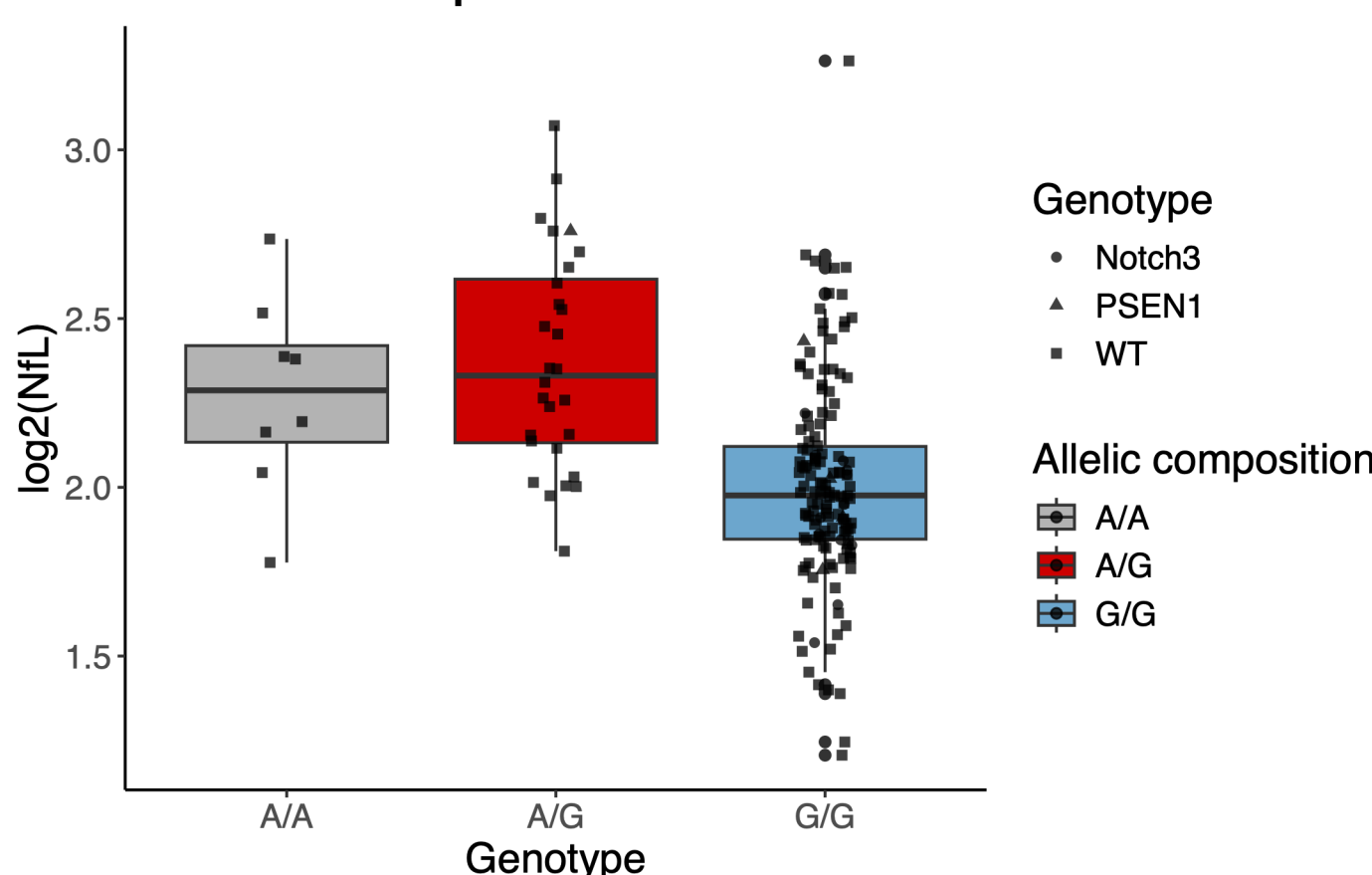


Fig. 3: Individuals homozygous for the alternative (major) allele (G/G) show lower plasma NfL, whereas those who are heterozygous (A/G) and homozygous for the reference (minor) allele (A/A) show higher NfL levels.

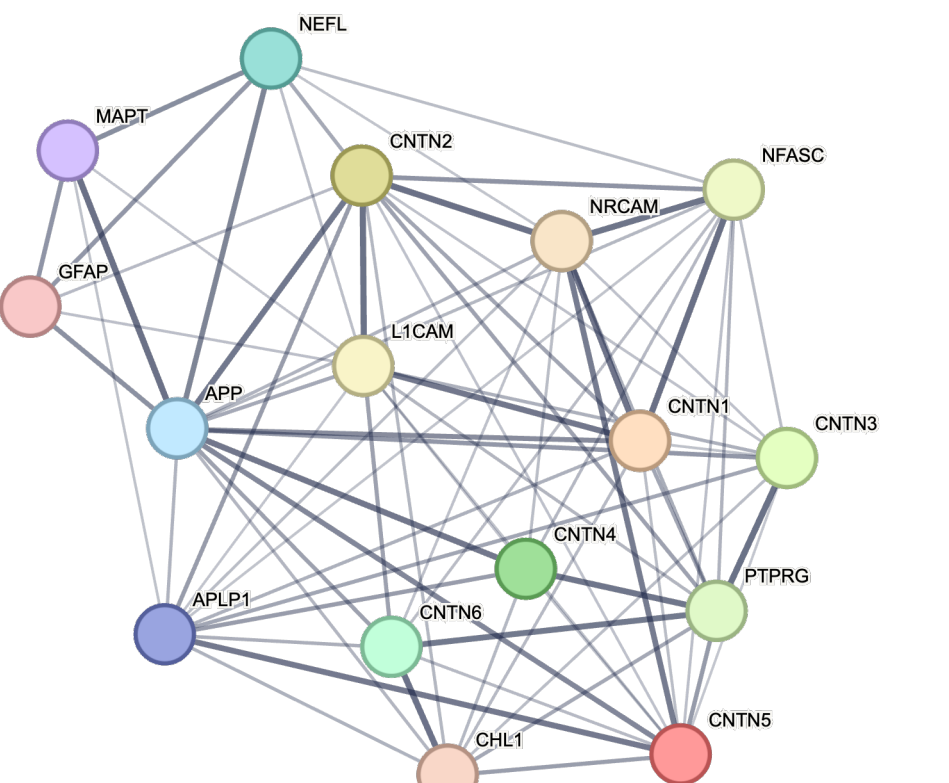


Fig. 4: STRING interaction network with nodes corresponding to proteins of interest (expanded to 5 interactors), and edges signifying evidence of interaction. Edge thickness indicates confidence.

3. Identified G/G variant shows lower NfL, higher CNTN5 levels in the brain

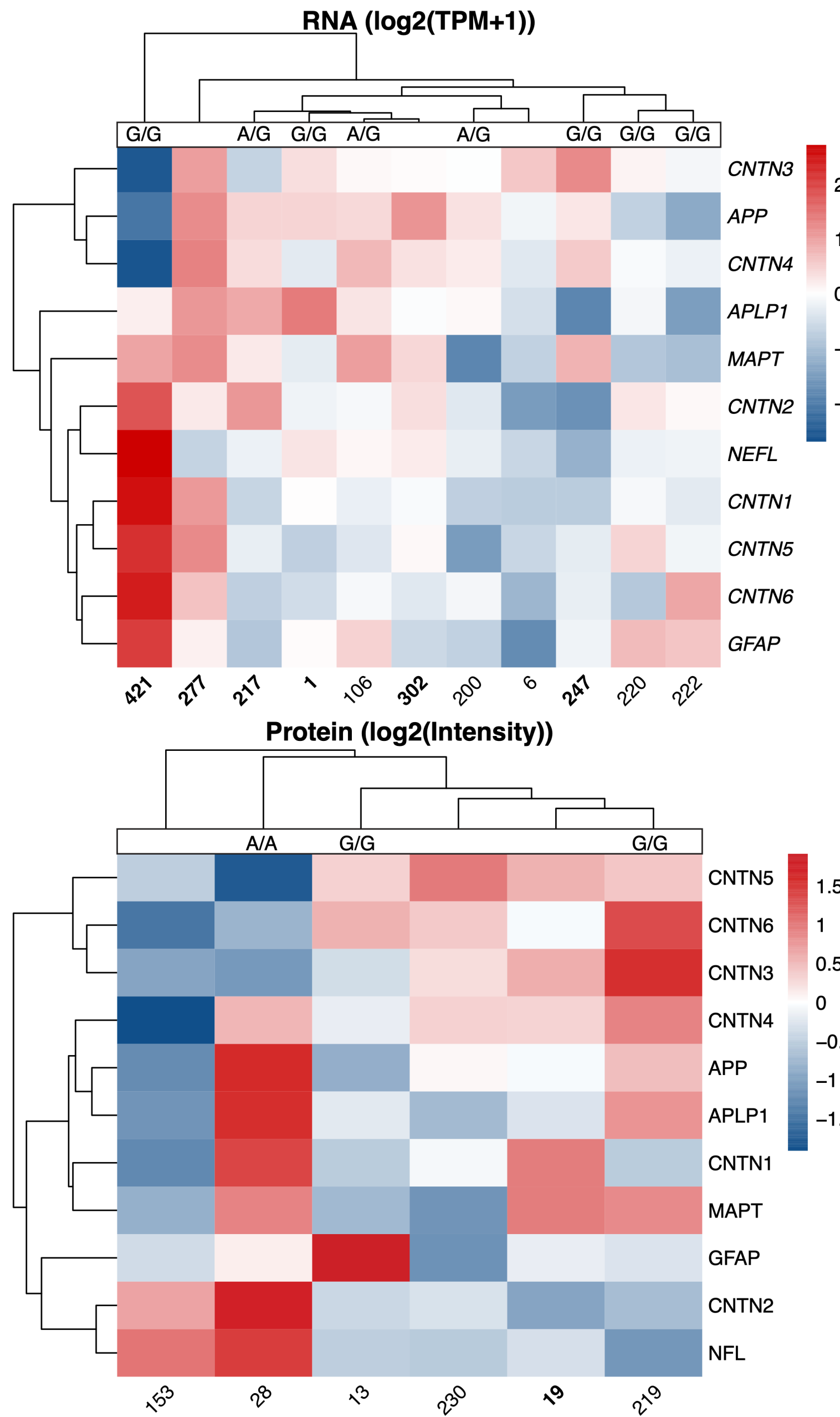
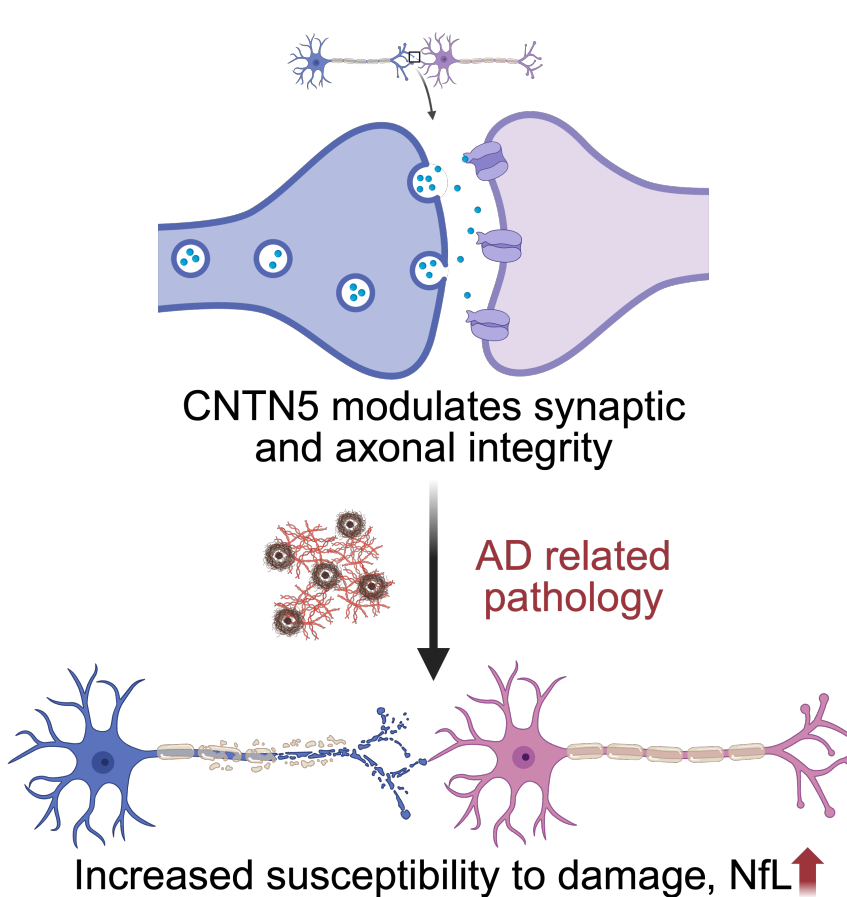


Fig. 5: Normalized brain RNA (top) and protein (bottom) levels for selected molecules on the right. Sample IDs are at the bottom, where males are in bold; with genotypes shown at the top. While no discernible trend can be seen at the RNA level, we see reduced NfL and higher CNTN5 with the G/G genotype, and vice versa for A/A.

CONCLUSIONS

- Our study demonstrates the utility of the common marmoset as a genetically mappable species; identifying disease-specific links even at comparatively lower sample sizes.
- While not directly affecting protein structure, a non-coding regulatory variant in *CNTN5* could potentially affect protein expression modulating neuronal circuitry. *CNTN5* is also known to interact with APP and APLP1, perhaps affecting APP processing and broader synaptic integrity.
- Next steps include expanding our analysis to the full colony and characterizing predicted variants in the context of human biology.



ACKNOWLEDGMENTS

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