Preclinical modelling in the mouse of altered neuroinflammation in AD-DS

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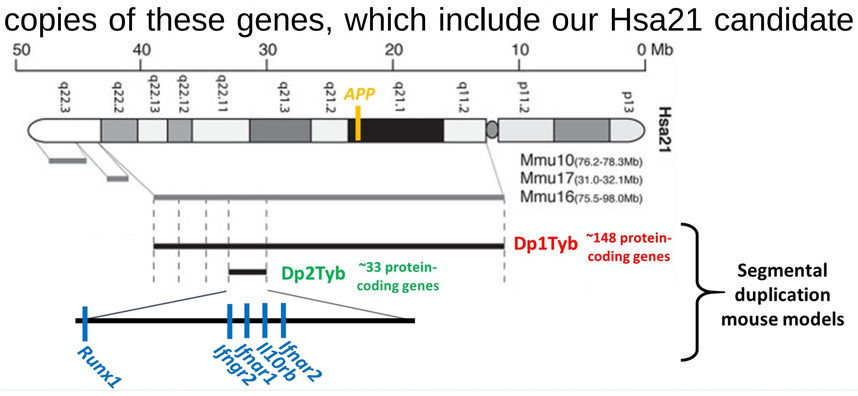
INTRODUCTION

People with Down syndrome (DS) develop Alzheimer's disease (AD) pathology, amyloid plaques and neurofibrillary tangles, by age 40 and the majority will develop dementia, due to having three copies of the chromosome 21 (Hsa21) gene *APP* leading to raised Aβ. How three copies of the other Hsa21 protein-encoding genes affects AD is unclear (1). Neuroinflammation, an important aspect of AD, is changed in people with DS, and people with DS have perturbations to their immune system, including elevated proinflammatory cytokine levels and an over-activated interferon response (2,3). Several genes on Hsa21 have been implicated in inflammation differences in DS, but how these genes when in three copies modify neuroinflammation in AD-DS is unknown. We are investigating how an extra copy of five Hsa21 candidate genes (*RUNX1, IFNAR1, IFNAR2, IFNGR2*, and *IL10RB*) modify neuroinflammation in response to Aβ.

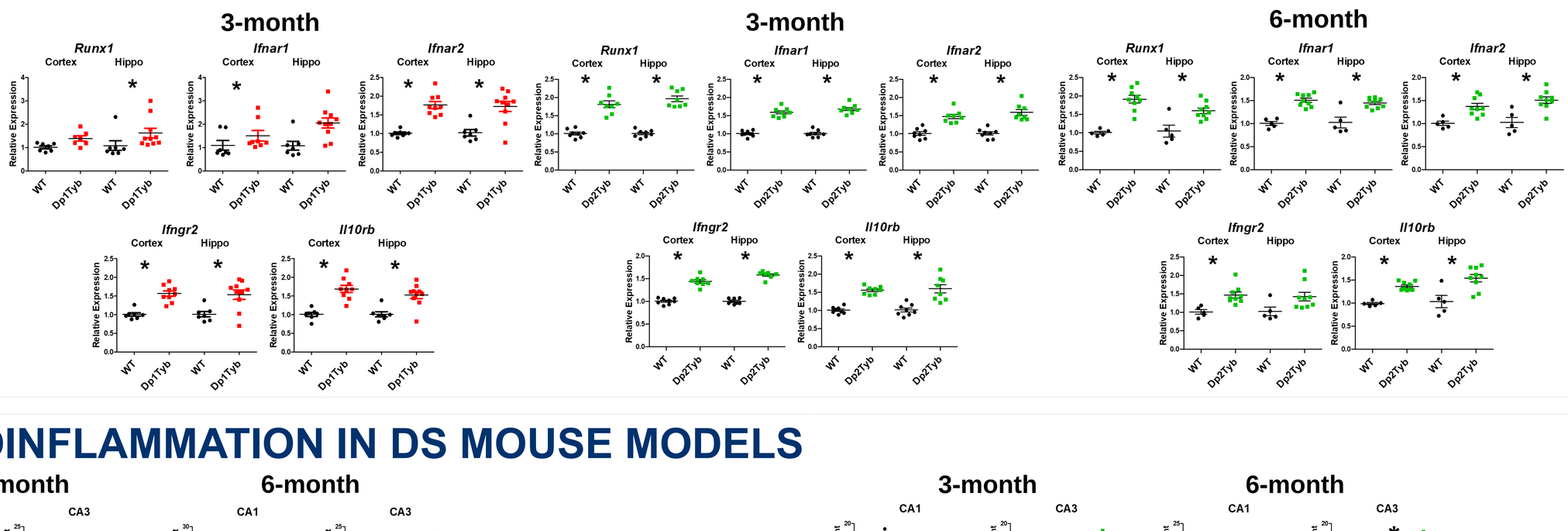
MODELS & METHODS

The homologous regions of Hsa21 are spread across mouse chromosomes (Mmu) 10, 16 and 17. The Dp1Tyb mouse model has a duplication on one chromosome of the region on Mmu16 syntenic to Hsa21, containing ~176 protein-coding Hsa21 orthologous genes. The Dp2Tyb mouse model has a duplication of a smaller Mmu16 subregion, containing ~35 protein-coding Hsa21 orthologous genes (5). Thus, these mice have three copies of these genes, which include our Hsa21 candidate genes for modifying neuroinflammation. Expression level of Hsa21 candidate genes was assessed with qPCR. Microglial counting in subregions of hippocampus was done with IBA1/DAPI staining. Quantification of proinflammatory cytokines was done with Meso Scale Discovery immunoassay.

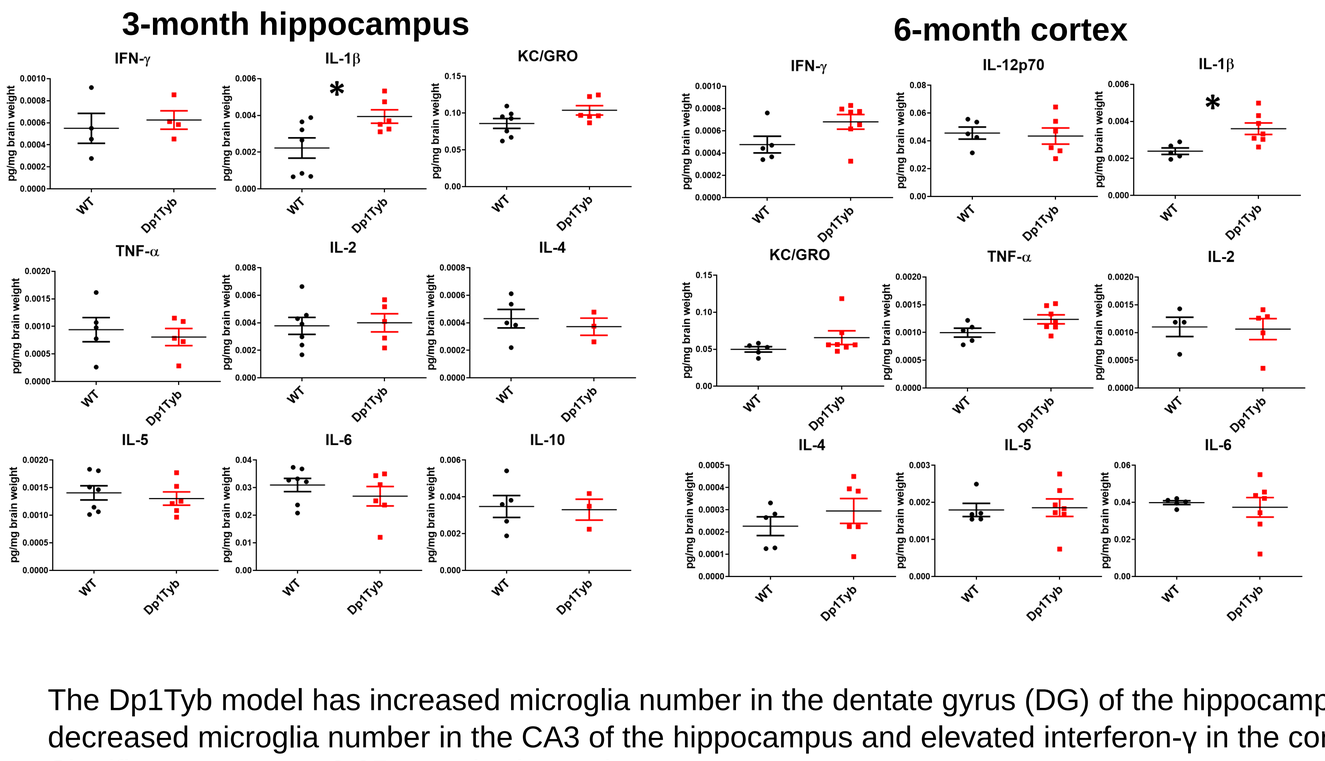


ELEVATED EXPRESSION OF HSA21 CANDIDATE GENES IN DS MOUSE MODELS

Hsa21 candidate genes have elevated mRNA expression when in three-copies in the Dp1Tyb and Dp2Tyb models, making them suitable models in which to study the effect of three copies of these genes. Univariate ANOVA, factors sex and genotype. Significance star $p < 0.05$, standard error bars.



ALTERED NEUROINFLAMMATION IN DS MOUSE MODELS



The Dp1Tyb model has increased microglia number in the dentate gyrus (DG) of the hippocampus and elevated levels of IL-1β. The Dp2Tyb model has decreased microglia number in the CA3 of the hippocampus and elevated interferon-γ in the cortex. Univariate ANOVA, factors sex and genotype. Significance star $p < 0.05$, standard error bars.

CONCLUSION

Interferon-γ is an activator of microglia (4), and people with DS have hyper-sensitivity to interferons due to three copies of genes *IFNAR1, IFNAR2, IFNGR2*, and *IL10RB* which encode subunits of the interferon receptors (2,3). Dp2Tyb mice have elevated interferon receptor levels and interferon-γ in the brain, consistent with the occurrence of type-2 interferon feed-forward mechanism. This may modify the microglial response to Aβ. Next, to test this we will cross the Dp2Tyb strain with the *App*$^{NL-G-F}$ knock-in model of amyloid pathology (6).

REFERENCES

1. Wiseman FK et al. Nat Rev Neurosci. 2015;16(9):564-574. doi:10.1038/nrn3983
2. Sullivan KD et al. Elife. 2016;5:e16220. doi:10.7554/eLife.16220
3. Sullivan KD et al. Sci Rep. 2017;7(1):14818. doi:10.1038/s41598-017-13858-3
4. Wu C et al. J Immunol. 2014;193(6):3036-3044. doi:10.4049/jimmunol.1302379
5. Lana-Elola E et al. Elife. 2016;5:e11614. doi:10.7554/eLife.11614
6. Saito T et al. Nat Neurosci. 2014;17(5):661-663. doi:10.1038/nn.3697

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