Knock-in mouse model, App$^{NLF/NLF}$, with slow plaque development into old age, shows plaque specific gene expression pattern more similar to that found in post-mortem tissues from people with Alzheimer's disease.

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Introduction

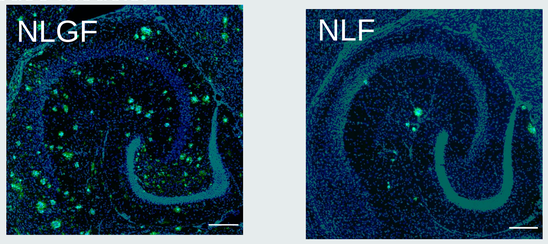
The APPKI mice NLF and NLGF (Saito et al., 2014) are widely used.

NLGF mouse (like many transgenic mice): an aggressive model laying down plaques rapidly from 2 months.

NLF mouse (more like progression of preclinical Alzheimer's disease): earliest plaques in middle age (around 9 months);slow progression into old age.

New technologies Nanostring GeoMx regional transcriptomics allows study of more relevant.

Age an important factor in gaining translational insites in mouse models.

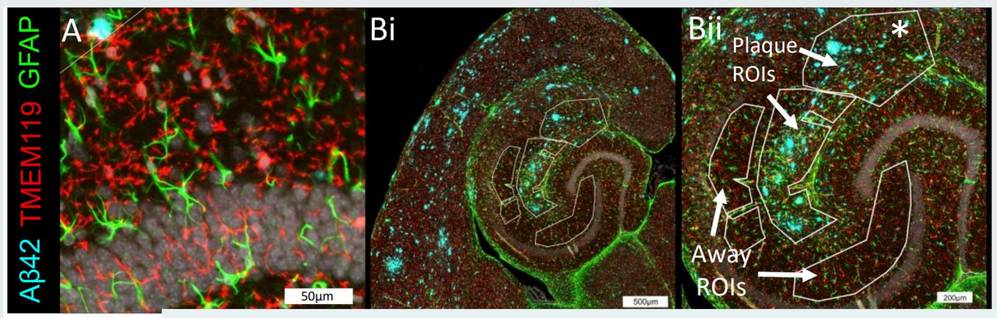


Methods: Whole hippocampal RNA was extracted from WT, NLF and NLGF mice (n=9-12/genotype; mixed sex; 18 months old).

RNAseq: Differential expression analysis compared WT to NLF or NLGF using DESeq2 R package, batch effect was accounted for as needed.

Regional cell-type enriched transcriptomics. Nanostring GeoMx technology: AOIs microglia, astrocytes (and underlying synapses) on, near or far from plaques

Comparing regions with dense plaques (**Plaque ROIs)** to regions away from plaques (**Away ROIs**) (n=6, 4 female, 2 male). Analysed using the limma-voom pipeline; within tissue pairing from plaque versus away.

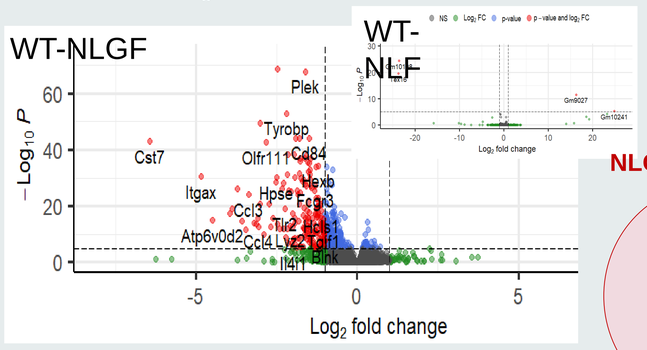


RNA-Seq from whole hippocampus only useful for NLGF:

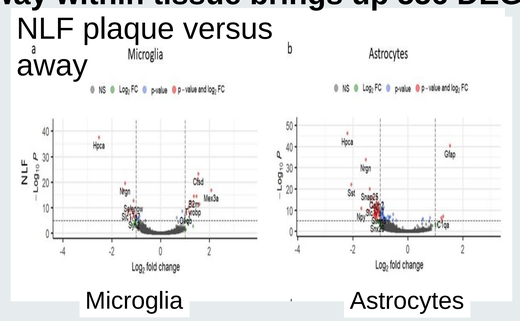
 # Differentially expressed genes (DEGs)

WT vs NLGF 2410

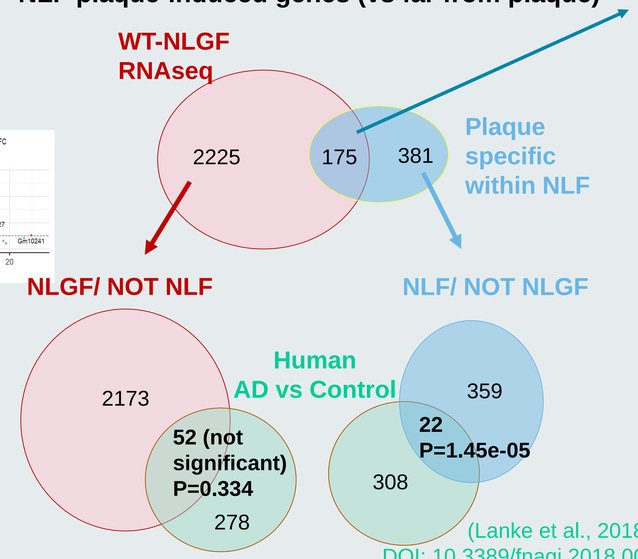
WT vs NLF ~5 genes NS functional enrich't



NLF: Regional cell-enriched transcriptomics: comparing paque and away within tissue brings up 556 DEGs



NLGF plaque-induced genes (versus WT) compared to NLF plaque-induced genes (vs far from plaque)



(Lanke et al., 2018 DOI: 10.3389/fnagi.2018.001

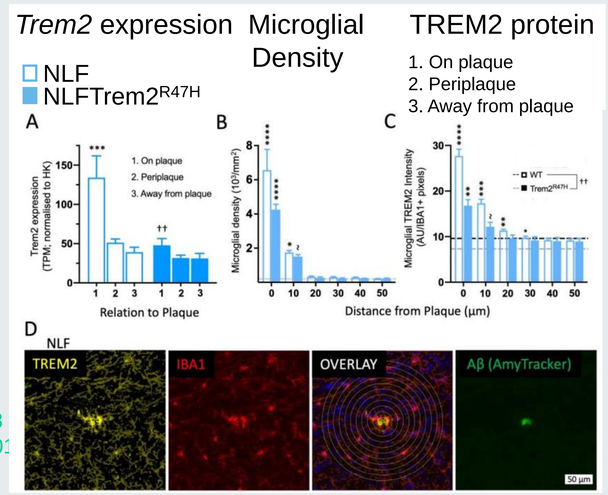
	1	2	3	4	5	6	7
AMPH			■			■	
ANK2,3		■	■			■	
BSN			■			■	
CACNG8	■	■			■		
CAMK2B	■	■			■		
CNIH2	■	■					
COX4I1				■			
COX5B, COX6A1, COX6B1, COX6C, COX8A				■			■
CPLX1			■	■		■	
CPNE6			■			■	
DLG2	■	■	■		■	■	
ERC2			■				
FKBP1A		■	■				
GABRA5			■			■	
GRIA1, GRIA2	■	■	■		■	■	
GRIN2A	■	■	■		■	■	
HPCA		■					
KCNIP2			■			■	
KCNQ2			■			■	
KIF1B			■				
LIN7B			■				
MAPK8IP2	■	■			■		
MINK1	■	■	■			■	
NDUFA4			■				■
NDUFAB1			■				■
NDUFB9							■
NDUFS5							■
NEFL	■	■			■		
NETO1	■	■					
NPTX1	■		■			■	
NPTXR	■						
NPY			■			■	
PLP1			■			■	
PRRT1	■	■					
PTK2B					■		
RIMBP2			■				
RIMS1			■				
SHISA6	■	■	■				
SLC12A4, SLC17A7, SLC1A2			■			■	
SNCA,B			■			■	
STX1A			■				
TSPOAP1			■				

NLF-plaque exclusive genes enriched for synaptic and mitochondrial functions

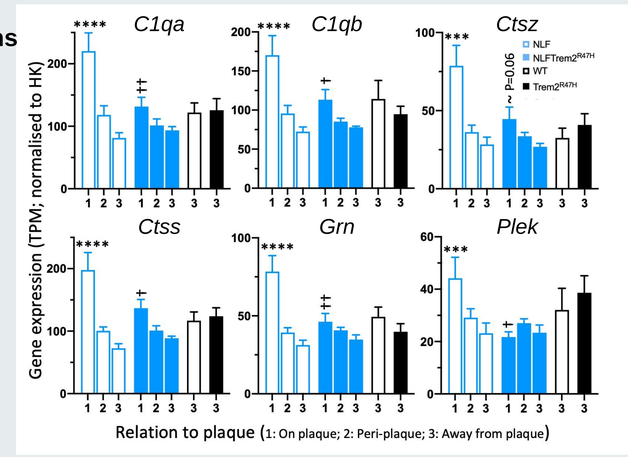
BIOLOGICAL FUNCTIONS
1. regulation of neurotransmitter receptor activity (GO:0099601)
2. regulation of cation channel activity (GO:2001257)
3. chemical synaptic transmission (GO:0007268)
4. mitochondrial electron transport, cytochrome c to oxygen (GO:0006123)
5. regulation of NMDA receptor activity (GO:2000310)
6. anterograde trans-synaptic signaling (GO:0098916)
7. aerobic electron transport chain (GO:0019646)

Plaque-dependent Microglial gene modules coexpressing in NLF and NLGF mice similar to previously studied genotypes

Some microglial genes, including *Trem2*, only increase in expression <u>on plaque contact</u>.



A small subset are *Trem2*-genotype-dependent



Conclusion

The NLF mouse shows similarities to the human condition of Alzheimer's disease that makes it likely a more translatable model. The TREM2 dependent roles of microglia depend on the microglia touching the plaque and so must depend on a lipophilic ligand

Wood et al., Cell Reports (in press)

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