

Identification of plasma biomarkers of Gulf War Illness



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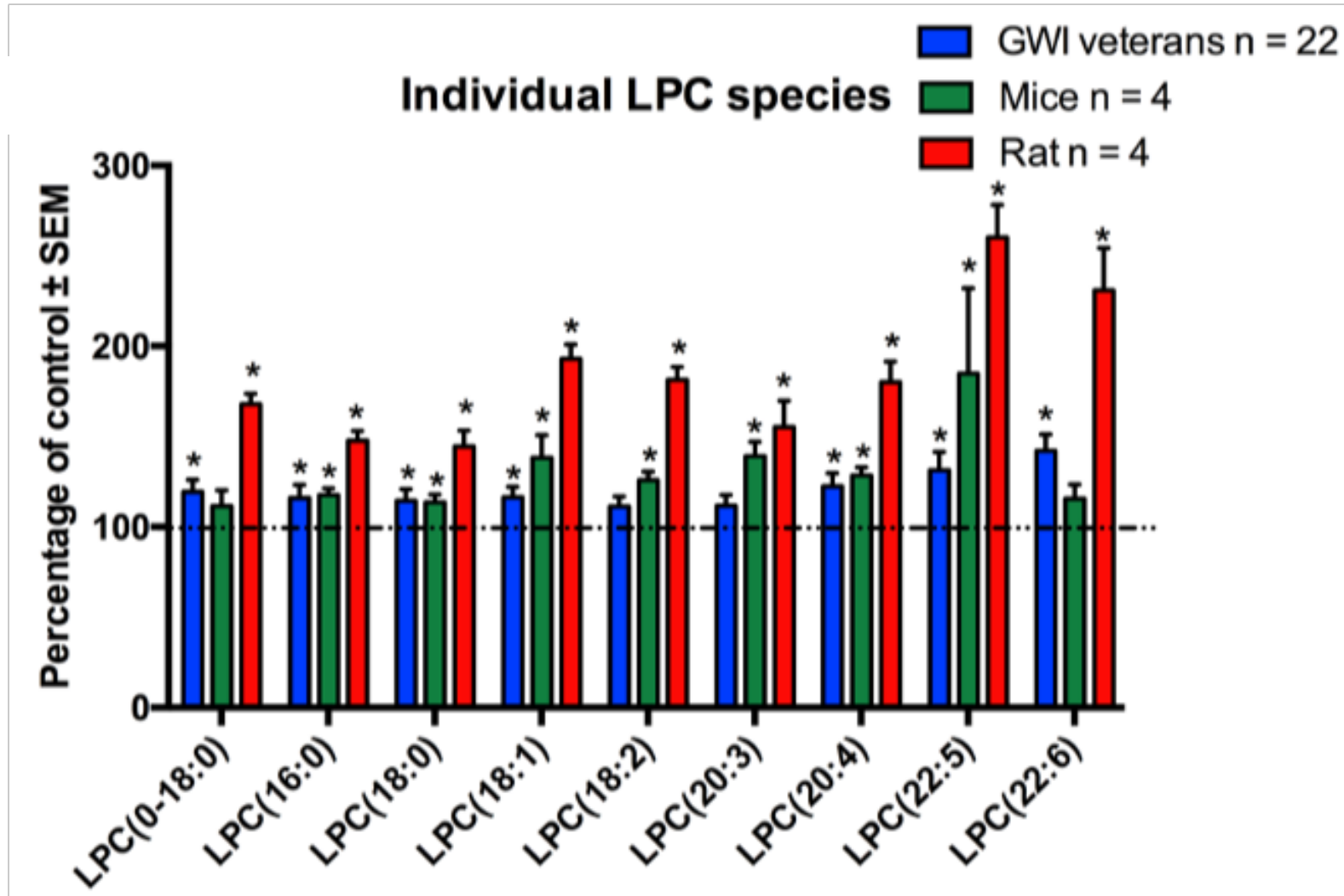
RACGWVI
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Our GWI Research Program Highlights

- PB+PER mouse model characterized to extended timepoints after exposure; neurobehavioral deficits and neuropathological changes.
- Proteomic analyses of the mouse model identifies Immune/inflammatory mechanisms, Mitochondrial dysfunction and Lipid Dysregulation.
- Translational approach –
 - Plasma profiles from well characterized GWI patients and controls – correlate profiles with clinical presentations
 - Plasma and brain analyses from mouse models
 - Common profiles as targets (biomarkers and therapeutics)
- Facilitated by collaborations between GWI clinical and basic science research teams.

Translational Relevance



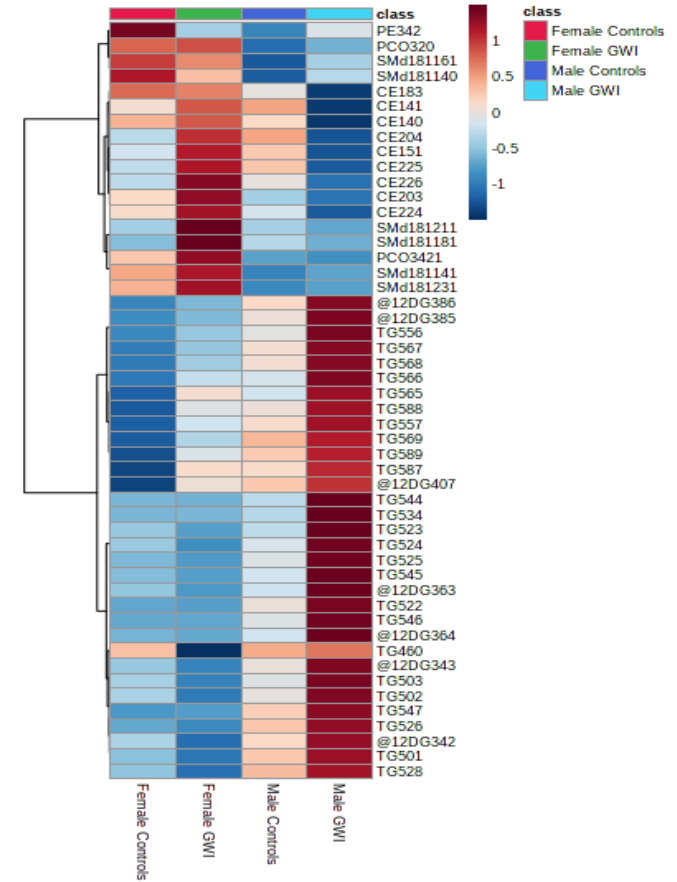
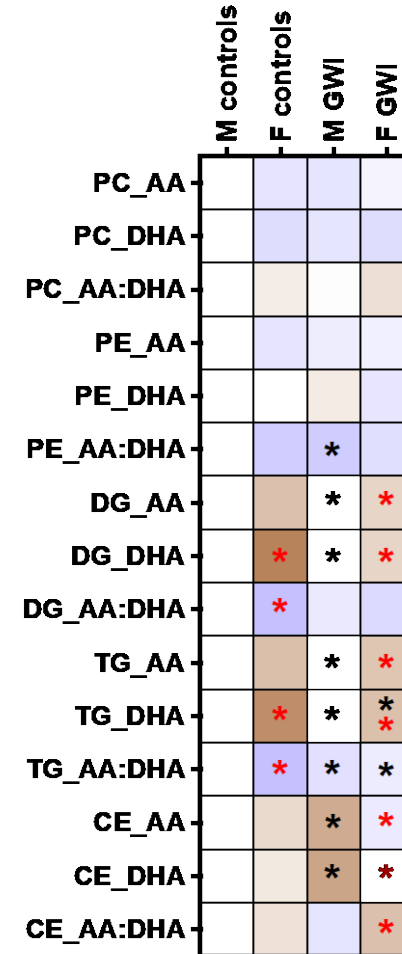
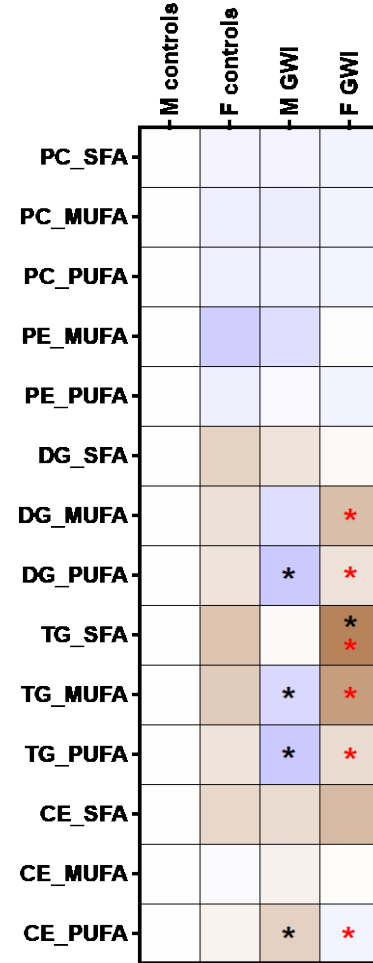
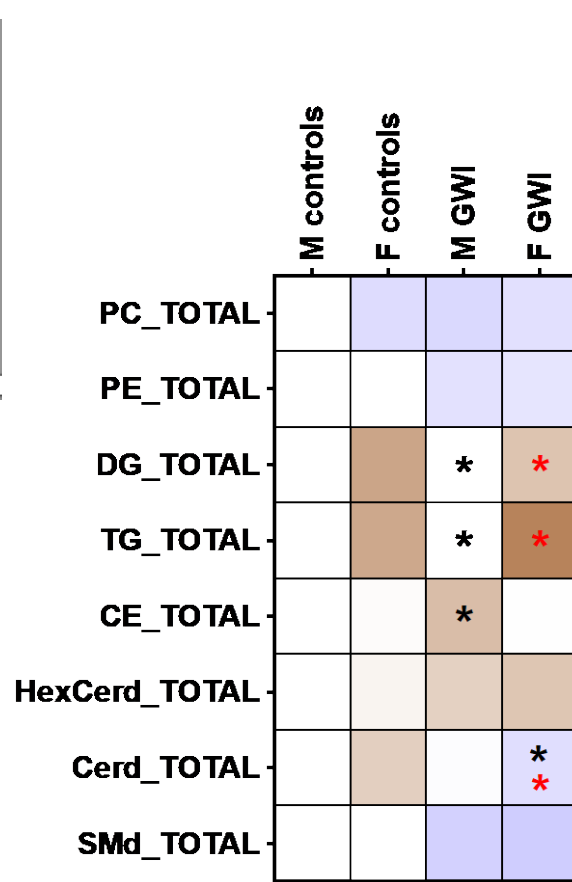
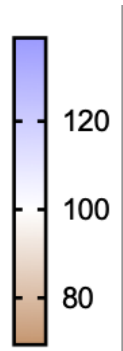


Study populations

- Cross-sectional design using plasma samples from 100 veterans with GWI (16 females).
 - Diagnosis of Kansas or the CDC criteria.
 - Inclusion criteria: symptoms in at least 3 of 6 symptom domains (fatigue/sleep problems, somatic pain, neurological/cognitive/mood symptoms, gastrointestinal symptoms, respiratory symptoms, and skin abnormalities).
 - Exclusion criteria: Diagnosis of other cognitive and/or mental health condition, systemic immune disorder, chronic obstructive pulmonary disease, malignancy or substance abuse.
- Plasma from 45 healthy controls (14 females) did not meet the GWI diagnostic criteria, were sedentary and matched to cases for age, sex, race/ethnicity.
- **Need full clinical picture for cases and controls - Medications? BMI?**
- APOE genotypes available for 135 participants
 - $\epsilon 4$ - control = 27, $\epsilon 4$ + control = 11, $\epsilon 4$ - GWI = 68 and $\epsilon 4$ + GWI = 29
- Oxylipin analyses available for 55 participants.



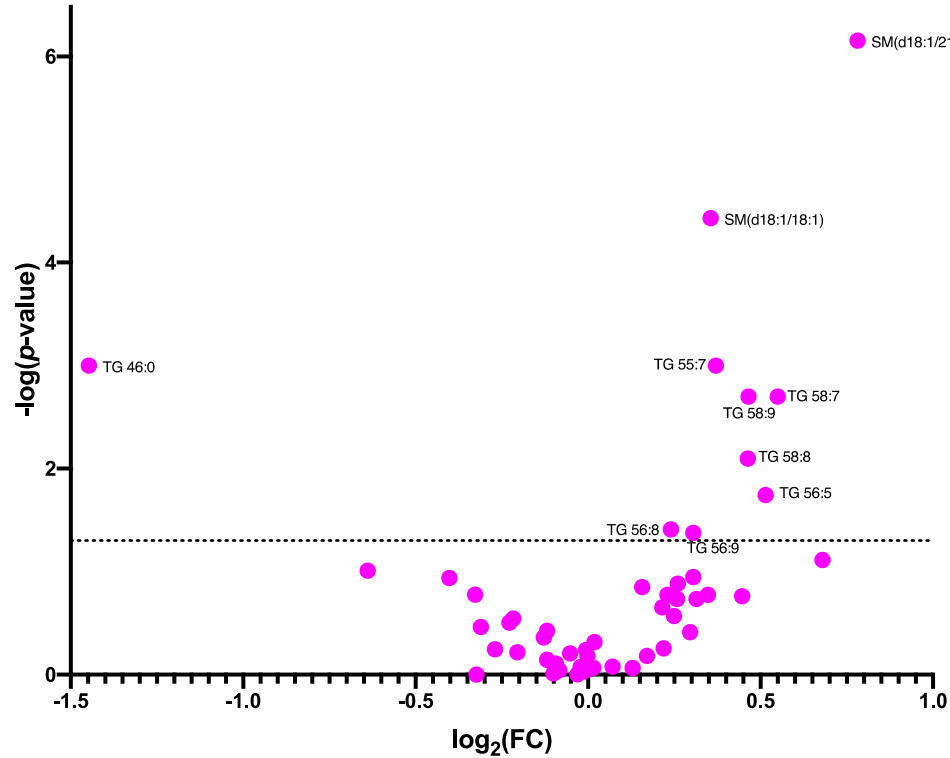
Heat maps showing lipid distributions, and hierarchical clustering



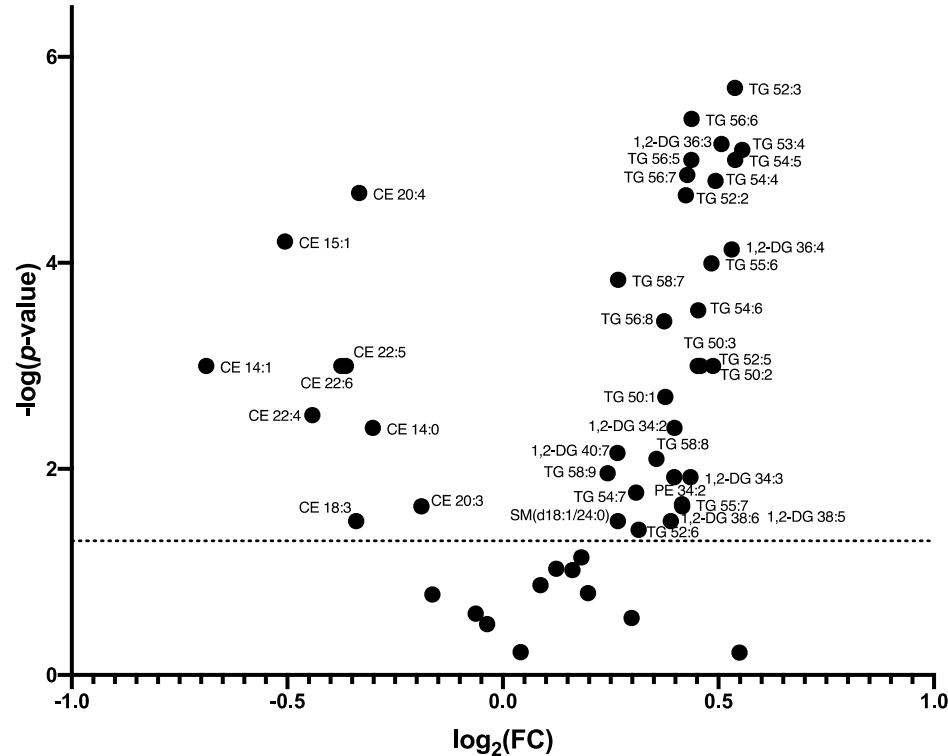


Overall greater lipid dysregulation in male GWI v control

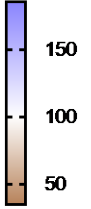
Female GWI v Control- Top 50 changing lipids from cluster analyses



Male GWI v Control- Top 50 changing lipids from cluster analyses

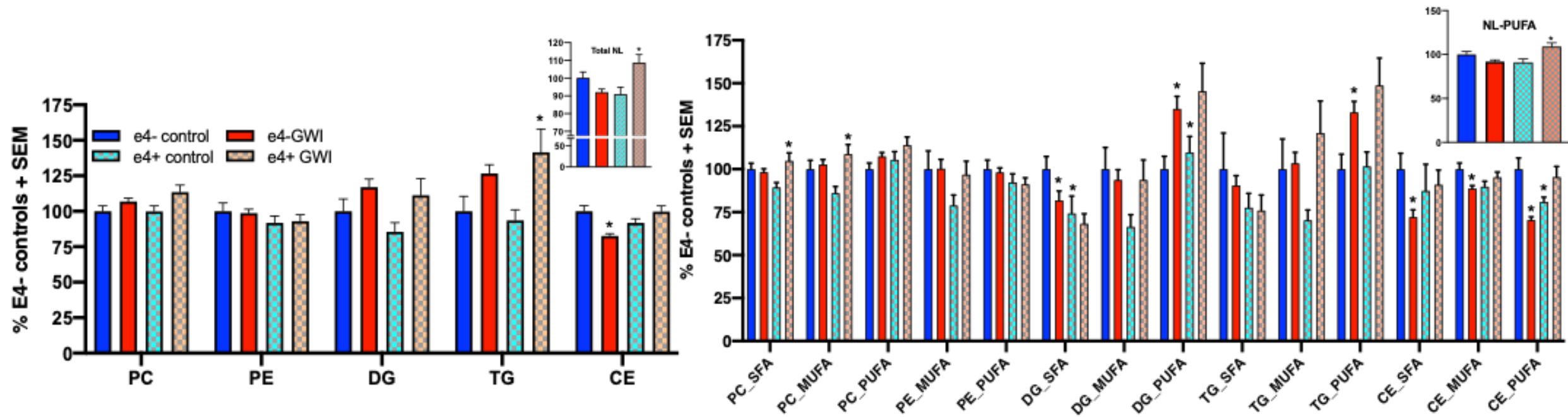


	M controls	F controls	M GWI	F GWI
12DG386		*	*	*
12DG385			*	*
TG565			*	*
TG587		*	*	*
TG556			*	*
TG567		*	*	*
TG566			*	*
TG569		*	*	*
TG528			*	*
12DG407		*	*	*
TG557		*	*	*
TG568		*	*	*
TG588		*	*	*
TG589		*	*	*
PE34:2		*	*	*
TG460			*	*
TG503			*	*
TG502			*	*
TG522			*	*
TG501			*	*
TG525			*	*
TG546			*	*
TG547		*	*	*
TG526		*	*	*
TG524			*	*
TG523			*	*
TG534			*	*
TG545			*	*
TG544			*	*
12DG342			*	*
12DG343			*	*
12DG363			*	*
12DG364			*	*
PCO3421		*	*	*
PCO320		*	*	*
SM(d18:1/21:1)		*	*	*
SM(d18:1/23:1)		*	*	*
SM(d18:1/24:1)				
SM(d18:1/26:1)				
SM(d18:1/24:0)			*	*
CE183			*	*
CE140			*	*
CE151			*	*
CE141			*	*
SM(d18:1/18:1)			*	*
CE203			*	*
CE224			*	*
CE226			*	*
CE204			*	*
CE225			*	*



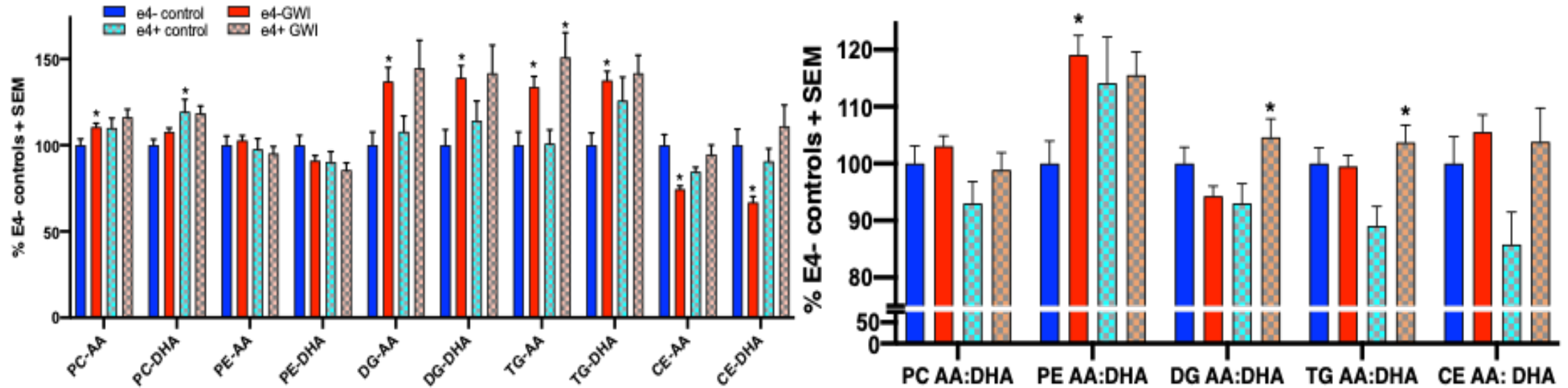


E4 carriers with GWI have elevated total TG and unsaturated neutral lipids



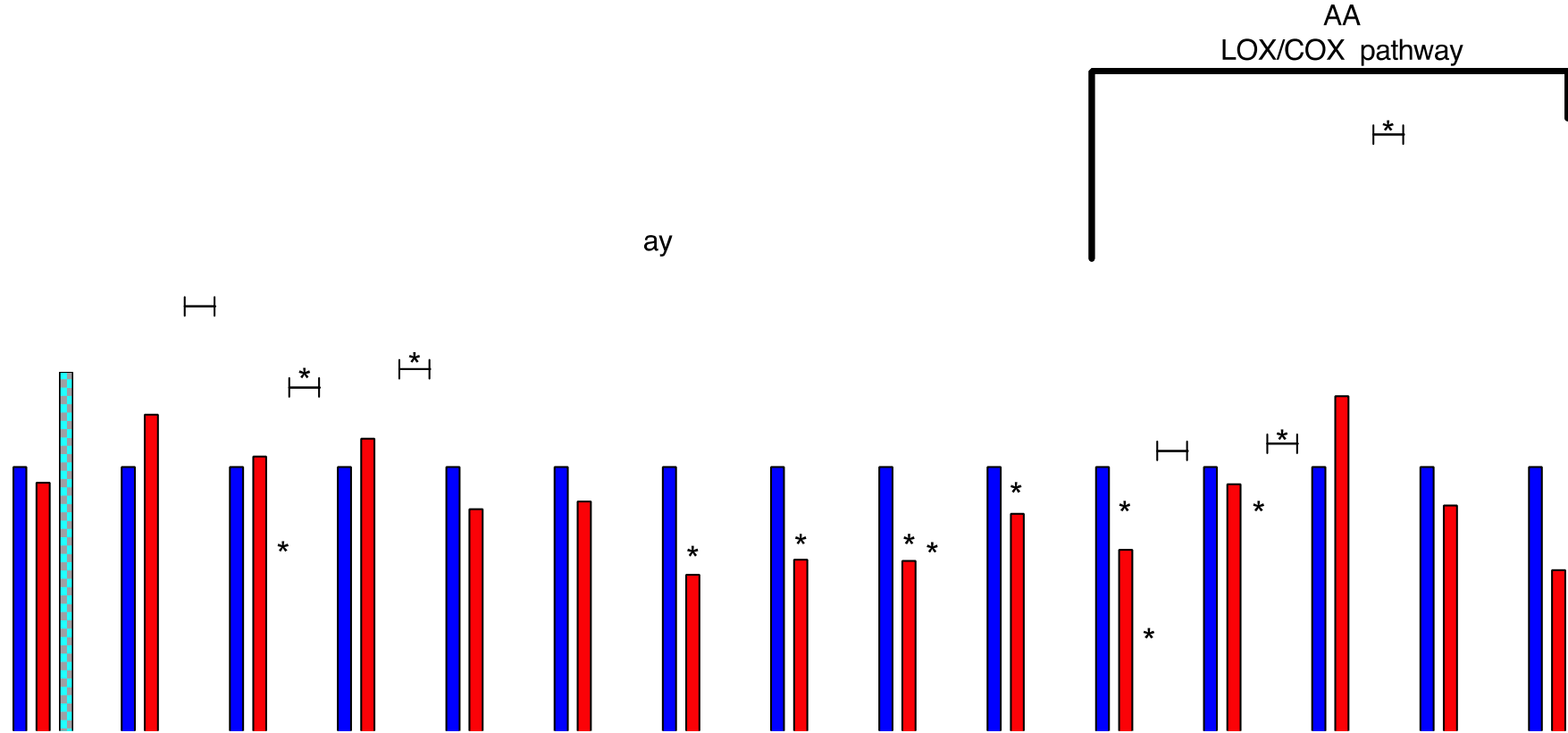


E4 carriers with GWI have elevated AA and DHA and an AA:DHA ratio imbalance in neutral lipids





E4 carriers with GWI have elevated CYP, sEH, LOX and COX derived oxylipins versus controls





Conclusions

- ◆ Abnormal lipid profiles in the blood of GWI veterans versus healthy controls
- ◆ These lipid profiles can be APOE genotype dependent
- ◆ Imbalances of AA:DHA (as seen in E4 GWI) are associated with inflammation and risk for Alzheimer's Disease and Related Disorders
- ◆ Lipid mediators derived from AA metabolism are elevated in E4 GWI
- ◆ Abnormal lipid profiles correspond with myeloid cell activation and neuroinflammation in our GWI mouse model
- ◆ Increased sample size and phenotypic subgrouping could lead to potential biomarker profiles
- ◆ **Targeting lipid dysregulation with therapeutic approaches**



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