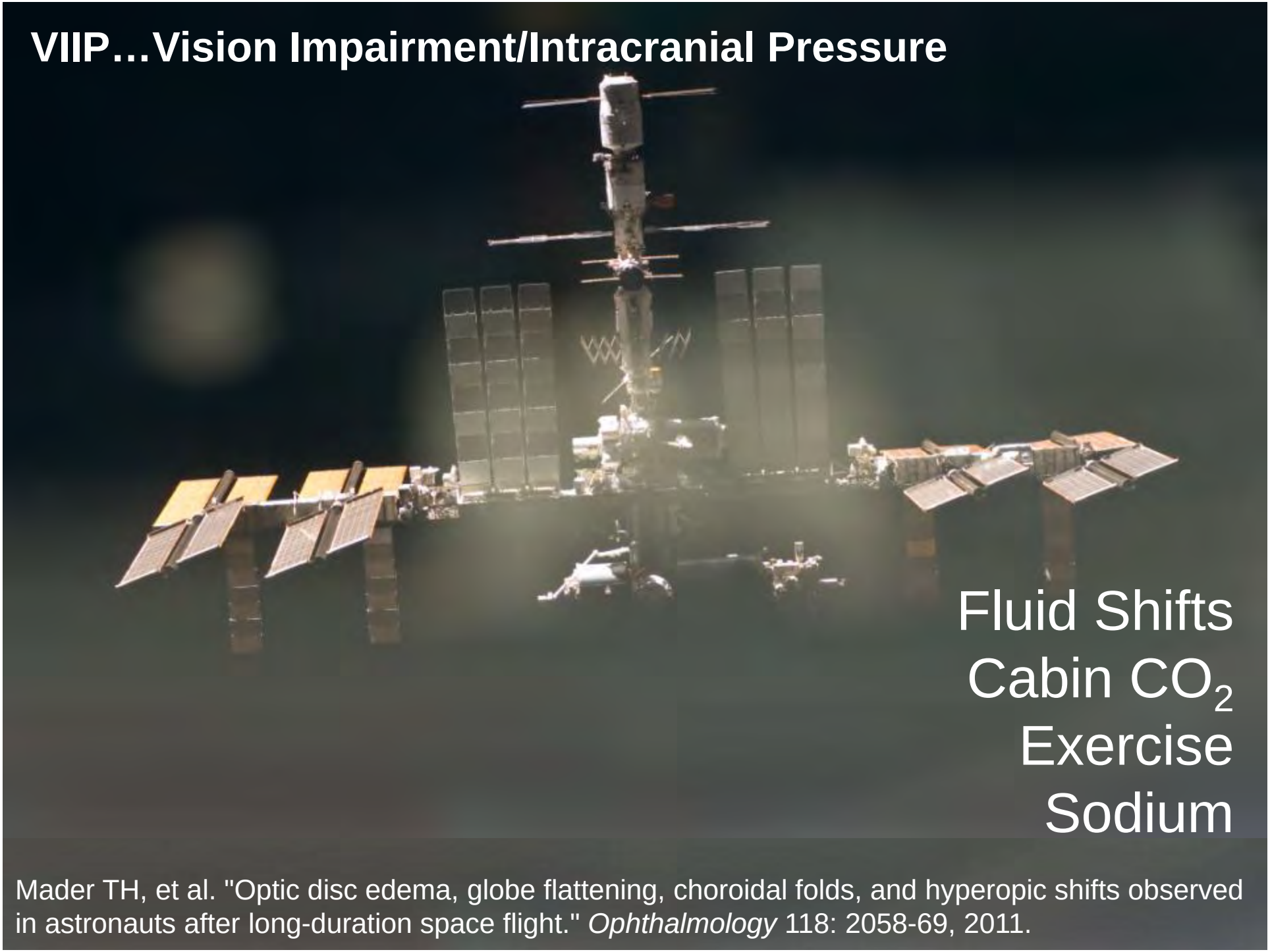
A potential pathway to understanding space flight vision issues

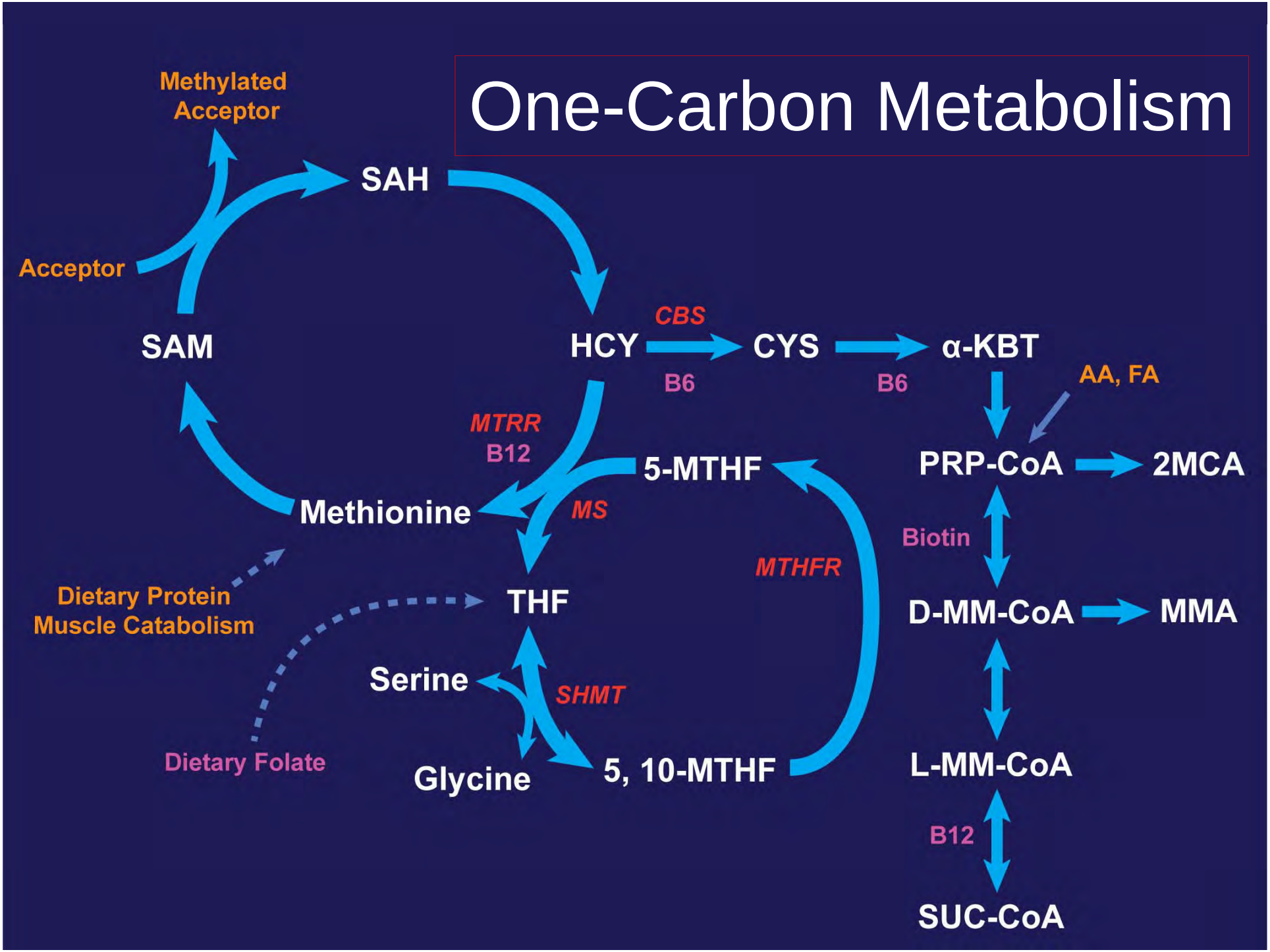
VIIP…Vision Impairment/Intracranial Pressure

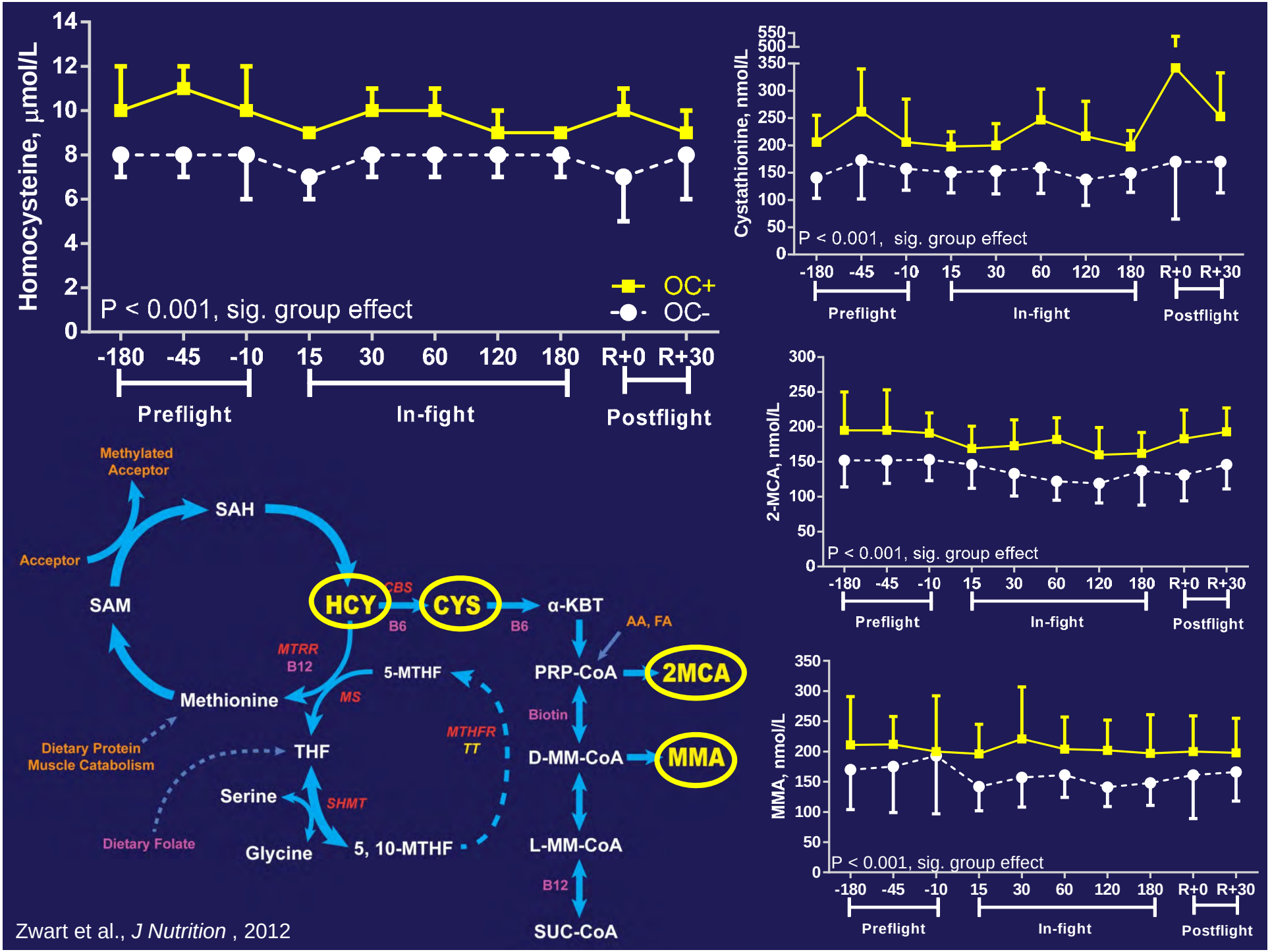


Fluid Shifts
Cabin CO_2
Exercise
Sodium

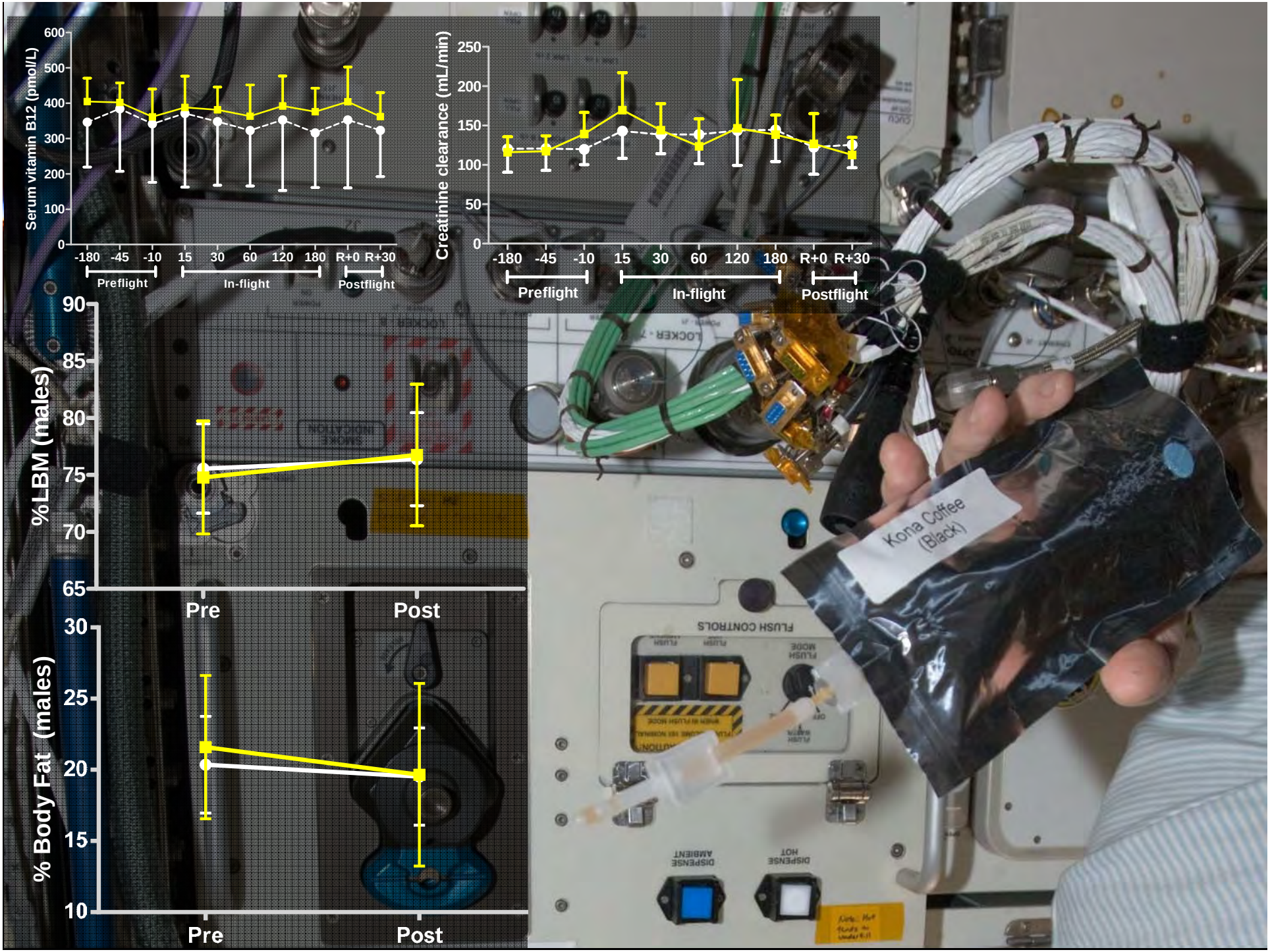
Mader TH, et al. "Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight." *Ophthalmology* 118: 2058-69, 2011.

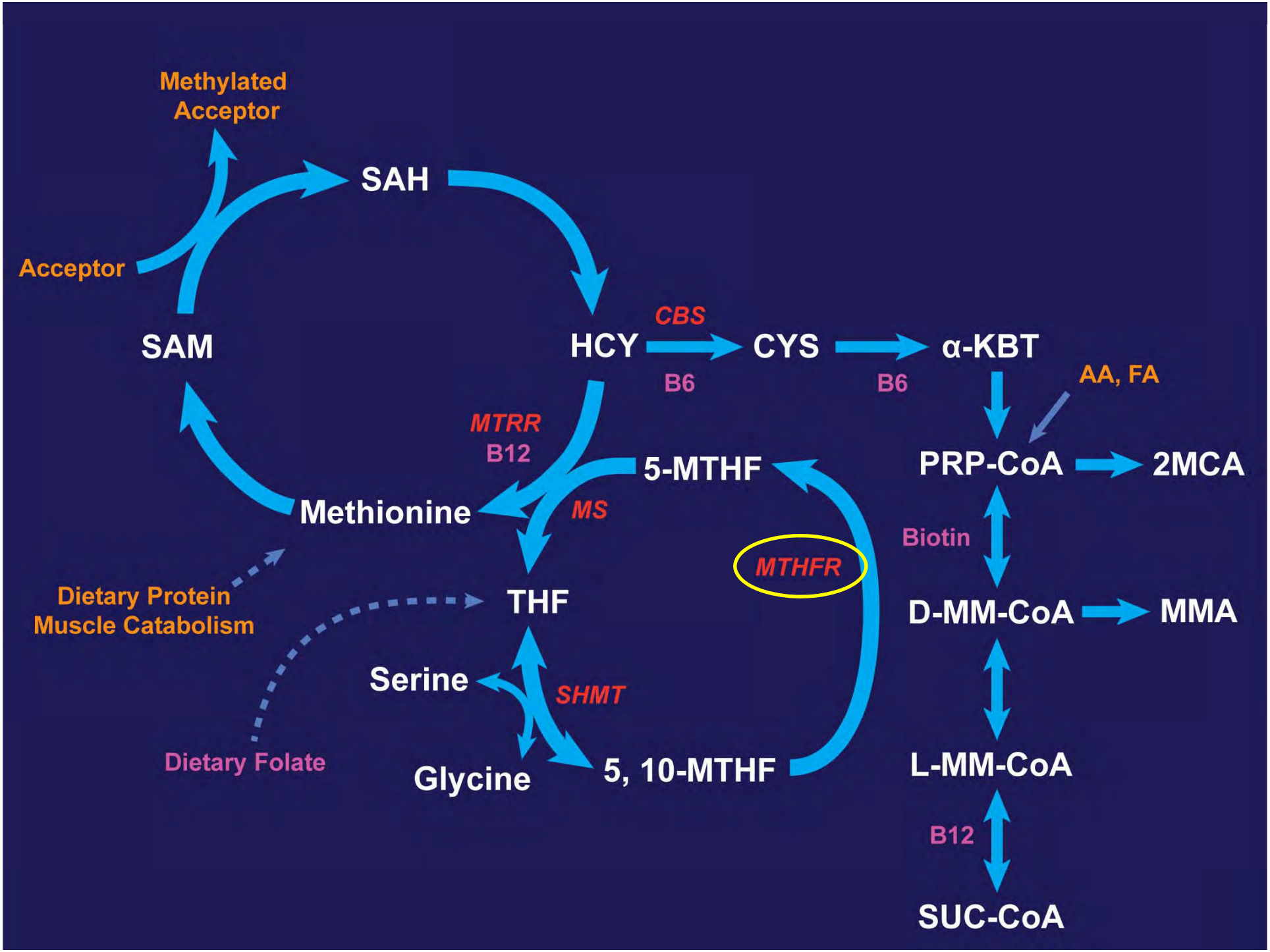
Nutritional Status Assessment SMO


One-Carbon Metabolism
Methylated Acceptor
SAH
Acceptor
SAM
HCY
CBS
B6
CYS
B6
α-KBT
AA, FA
PRP-CoA
2MCA
MTRR
B12
5-MTHF
MS
Methionine
Biotin
MTHFR
Dietary Protein
Muscle Catabolism
THF
D-MM-CoA
MMA
Serine
SHMT
Dietary Folate
Glycine
5, 10-MTHF
L-MM-CoA
B12
SUC-CoA

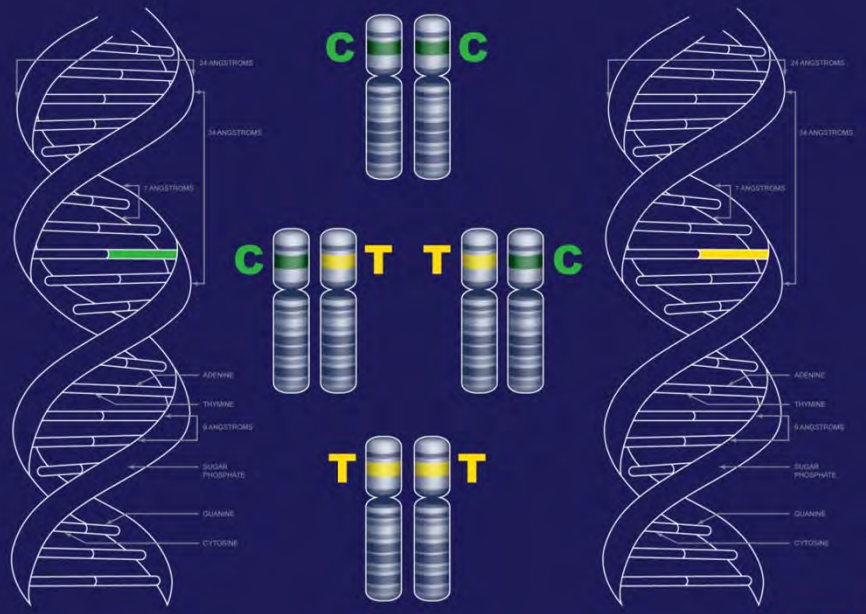


Zwart et al., *J Nutrition* , 2012

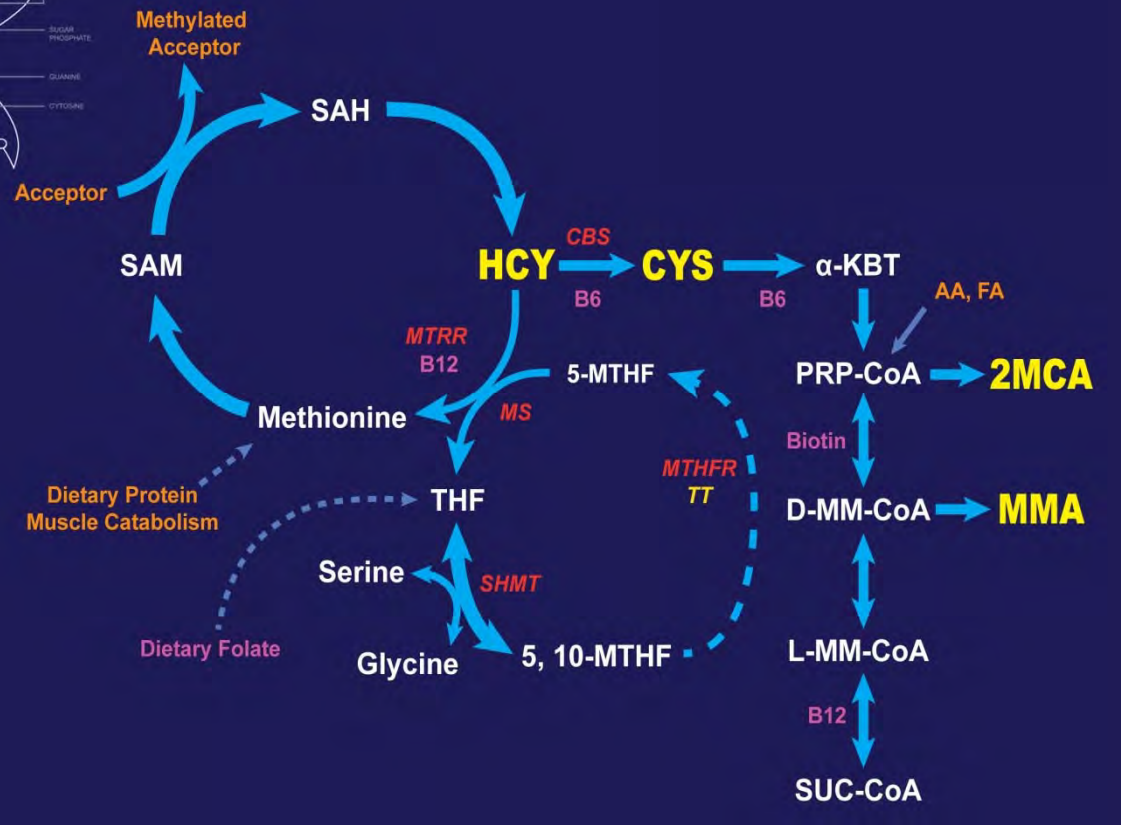

Serum vitamin B12 (pmol/L)
600
500
400
300
200
100
0
-180 -45 -10 15 30 60 120 180 R+0 R+30
Preflight
In-flight
Postflight
Creatinine clearance (mL/min)
250
200
150
100
50
0
-180 -45 -10 15 30 60 120 180 R+0 R+30
Preflight
In-flight
Postflight
%LBM (males)
90
85
80
75
70
65
Pre
Post
% Body Fat (males)
30
25
20
15
10
Pre
Post
Kona Coffee
(Black)
FLUSH CONTROLS
DISPENSE
AMBIENT
DISPENSE
HOT

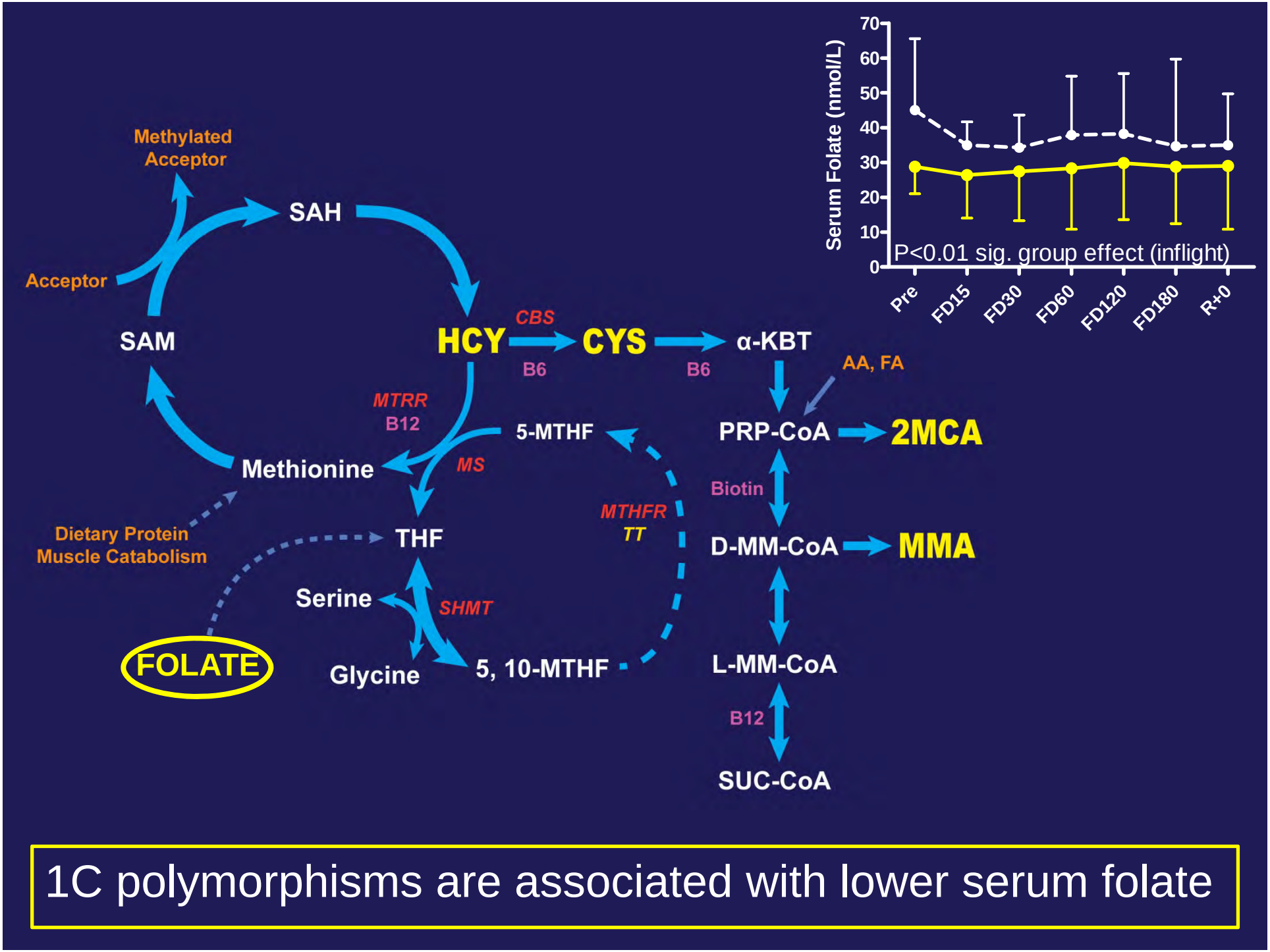

Methylated Acceptor
SAH
Acceptor
SAM
HCY
CBS
B6
CYS
B6
α-KBT
AA, FA
PRP-CoA
2MCA
MTRR
B12
5-MTHF
MS
Methionine
Biotin
MTHFR
Dietary Protein
Muscle Catabolism
THF
D-MM-CoA
MMA
Serine
SHMT
Dietary Folate
Glycine
5, 10-MTHF
L-MM-CoA
B12
SUC-CoA

MTHFR C677T Polymorphism

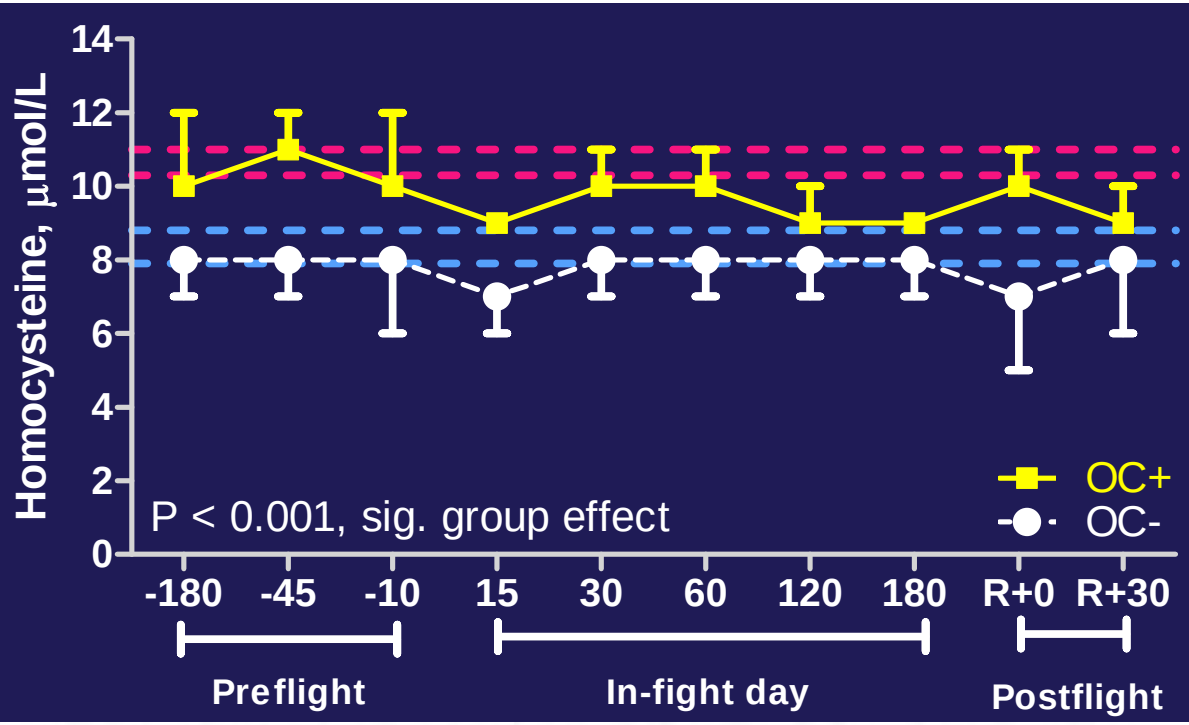


	% Pop	Enz Act.
C/C	~35%	100%
C/T(T/C)	~50%	~66%
T/T	~15%	~50%





1C polymorphisms are associated with lower serum folate



Plasma concentrations of one-carbon metabolites of women classified by their MTHFR 677C→T genotype at baseline and after 7 wk of dietary folate restriction (115 µg dietary folate equivalents/d)[1]

	C/C Baseline	C/C Restricted	C/C Change	T/T Baseline	T/T Restricted	T/T Change
Homocysteine, *µmol/L*	7.9 ± 0.4	9.7 ± 0.9	1.8 ± 0.9	11.0 ± 0.7†	14.5 ± 2.2	3.5 ± 2.2

Davis et al., *J Nutr* 2005

Table 2. Relationships between genotypes and tHcy

	tHcy, µM
MTHFR 677C>T	
CC	8.8 [4.2-29.5]
CT	8.7 [4.4-34.0]
TT	10.3 [5.9-44.6]
Anova*, *P*	< .0005†

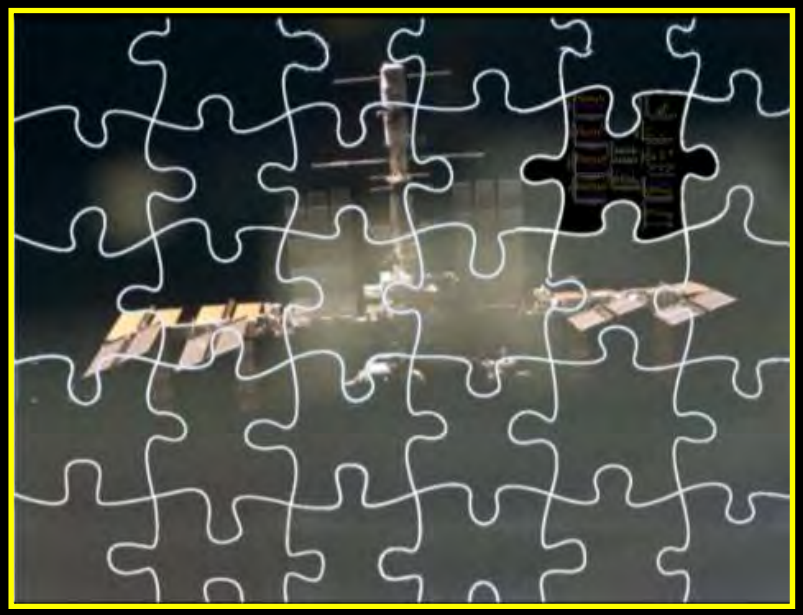
Kluijtmans et al., *Blood* 2003

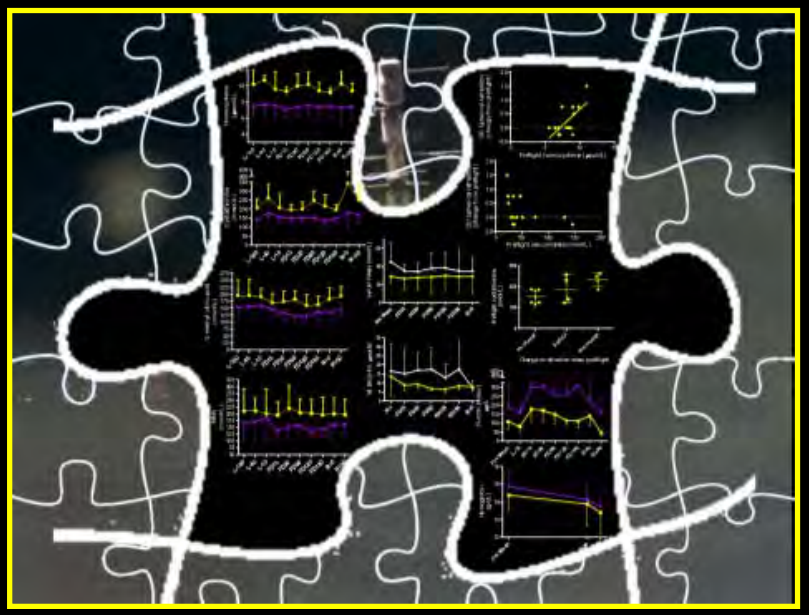
1C polymorphisms are associated with risk of vascular events/conditions, including:

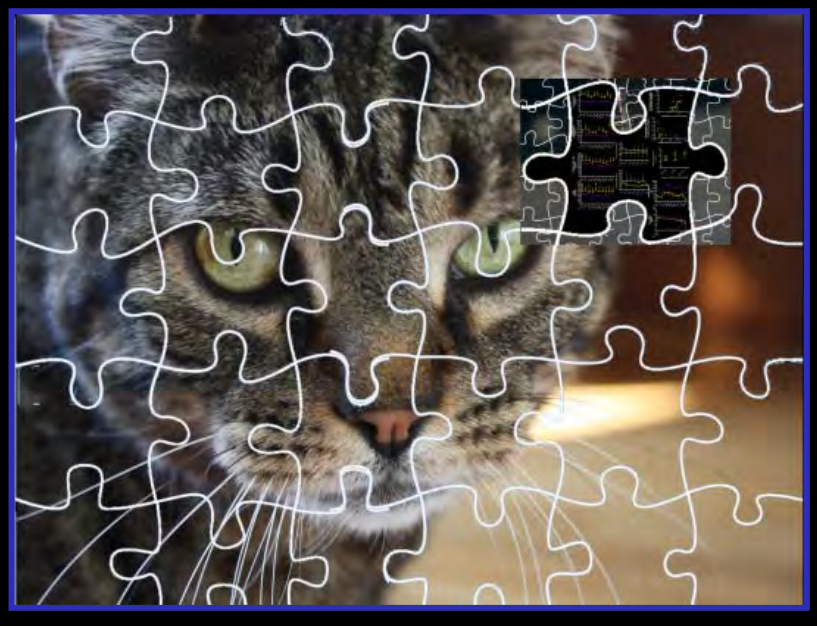
- stroke
- migraine
- narrower retinal vasculature (in men)

- Cases:
  - idiopathic intracranial hypertension and megaloblastic anemia case
  - folate or B12 repletion and optic neuropathy

These data suggest that one carbon polymorphism(s) may have a role in spaceflight-related vision changes.

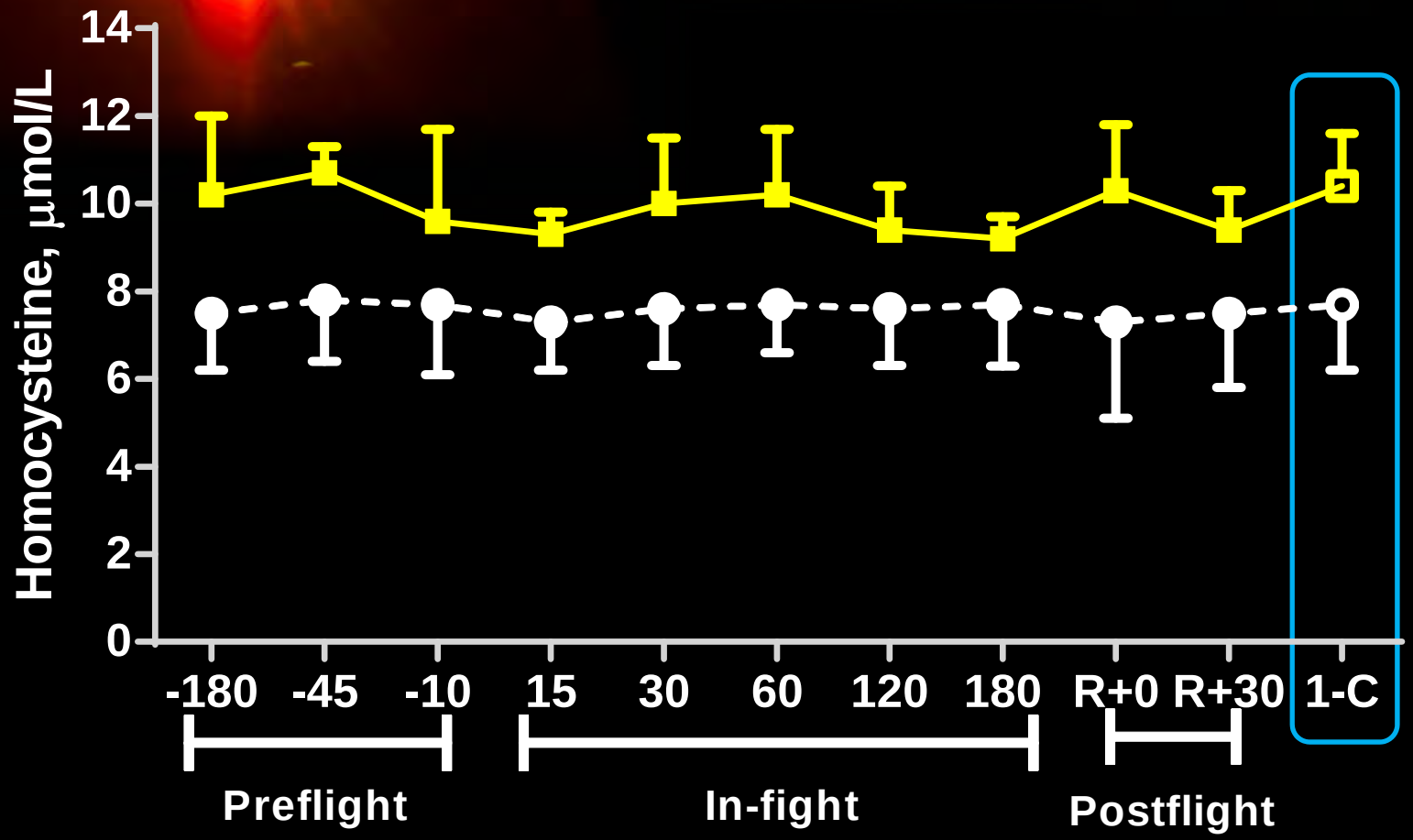






- Follow-on project…One Carbon Study
  - Five 1C polymorphisms
  - Expanded 1C biochemistry, vitamin status
  - Vision and related medical data
- Status
  - n = 70/72 potential astronauts (Exp 1-48…)
  - Analyses complete, medical data received in late May 2014.
  - Data analysis underway…
  - **Preliminary** findings follow…

One Carbon: Hcy Update



Optic Nerve Sheath Diameter

BRIEF REPORT

Correlation of Optic Nerve Sheath Diameter with Direct Measurement of Intracranial Pressure

Heidi Harbison Kimberly, MD, Sachita Shah, MD, Keith Marill, MD, Vicki Noble, MD

Abstract

Background: Measurements of the optic nerve sheath diameter (ONSD) using bedside ultrasound (US) have been shown to correlate with clinical and radiologic signs and symptoms of increased intracranial pressure (ICP).

Objectives: Previous literature has identified 5 mm as the ONSD measurement above which patients exhibit either clinical or radiologic signs of elevated ICP. The goals of this study were to evaluate the association between ONSD and ICP and to validate the commonly used ONSD threshold of 5 mm using direct measurements of ICP as measured by ventriculostomy.

Methods: A prospective blinded observational study was performed using a convenience sample of adult patients in both the emergency department (ED) and the neurologic intensive care unit (ICU) who had invasive intracranial monitors placed as part of their clinical care. Ocular USs were performed with a 10–5 MHz linear probe. Emergency physicians (EPs) with previous ocular US experience performed ONSD measurements while blinded to the contemporaneous ICP reading obtained directly from invasive monitoring. The association between ONSD and ICP was assessed with the Spearman rank correlation coefficient, and a receiver operator characteristic (ROC) curve was created to determine the optimal ONSD cutoff to detect ICP > 20 cm H_2O.

Results: Thirty-eight ocular USs were performed on 15 individual patients. Spearman rank correlation coefficient of ONSD and ICP was 0.59 ($p < 0.0005$) demonstrating a significant positive correlation. An ROC curve was created to assess the ability of ONSD to distinguish an abnormal ICP greater than 20 cm H_2O. The area under the ROC curve was 0.93 (95% confidence interval [CI] = 0.84 to 0.99). Based on inspection of the ROC curve, ONSD > 5 mm performed well to detect ICP > 20 cm H_2O with a sensitivity of 88% (95% CI = 47% to 99%) and specificity of 93% (95% CI = 78% to 99%).

Conclusions: Using an ROC curve the authors systematically confirmed the commonly used threshold of ONSD > 5 mm to detect ICP > 20 cm H_2O. This study directly correlates ventriculostomy measurements of ICP with US ONSD measurements and provides further support for the use of ONSD measurements as a noninvasive test for elevated ICP.

ACADEMIC EMERGENCY MEDICINE 2008; 15:201–204 © 2008 by the Society for Academic Emergency Medicine

Keywords: ultrasound, intracranial pressure, optic nerve sheath diameter

The diagnosis of elevated intracranial pressure (ICP) is both challenging and critical, because prompt recognition and treatment are essential to prevent possible brain damage or death. Bedside ocular ultrasound (US) is emerging as a noninvasive technique to detect elevated ICP. Increased ICP is transmitted to the subarachnoid space surrounding the optic nerve, causing optic nerve sheath expansion.[1] Measurement of the optic nerve sheath diameter (ONSD) has been studied in postmortem specimens,[2] intrathecal infusion models,[3] children with ventriculoperitoneal shunts,[4] and emergency department (ED) patients with head injuries.[5,6] In the clinical studies performed to date, ONSD has been correlated with clinical symptoms or computed tomography (CT) abnormalities, both surrogate indicators of elevated ICP.

Intracranial pressure can be definitively measured and monitored through placement of invasive monitoring devices such as an extraventricular drain (EVD).[7,8]

From the Department of Emergency Medicine, Massachusetts General Hospital (HHK, SS, KM, VN), Boston, MA.

Received July 30, 2007; revisions received September 10 and September 27, 2007; accepted September 30, 2007.

Presented at the Annual Meeting of the Society for Academic Emergency Medicine, May 16–19, 2007, Chicago, IL.

Address for correspondence and reprints: Heidi H. Kimberly, MD; e-mail: hkimberly@partners.org.

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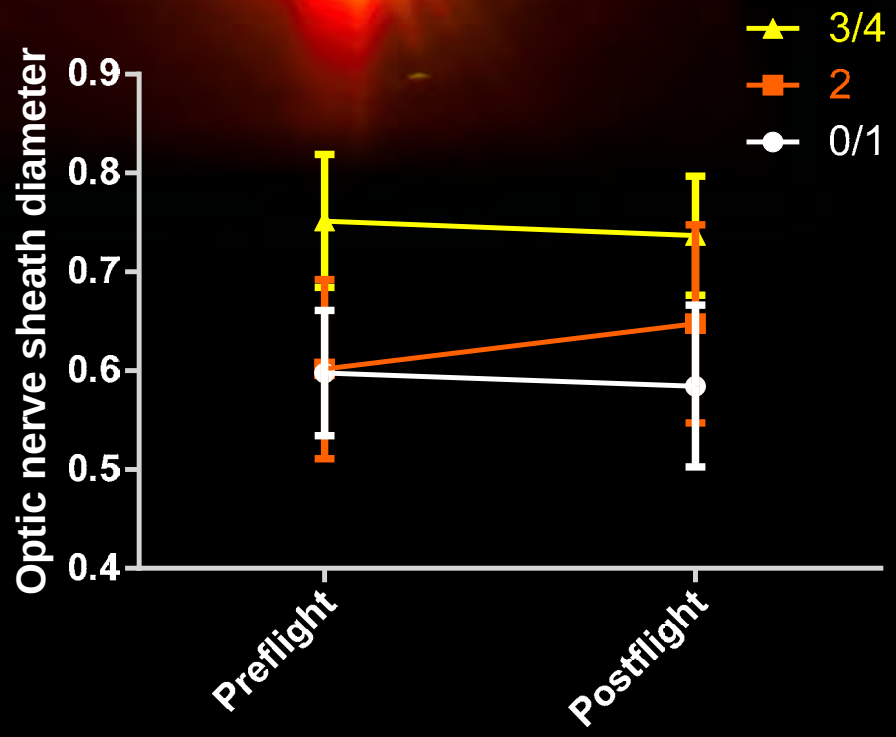
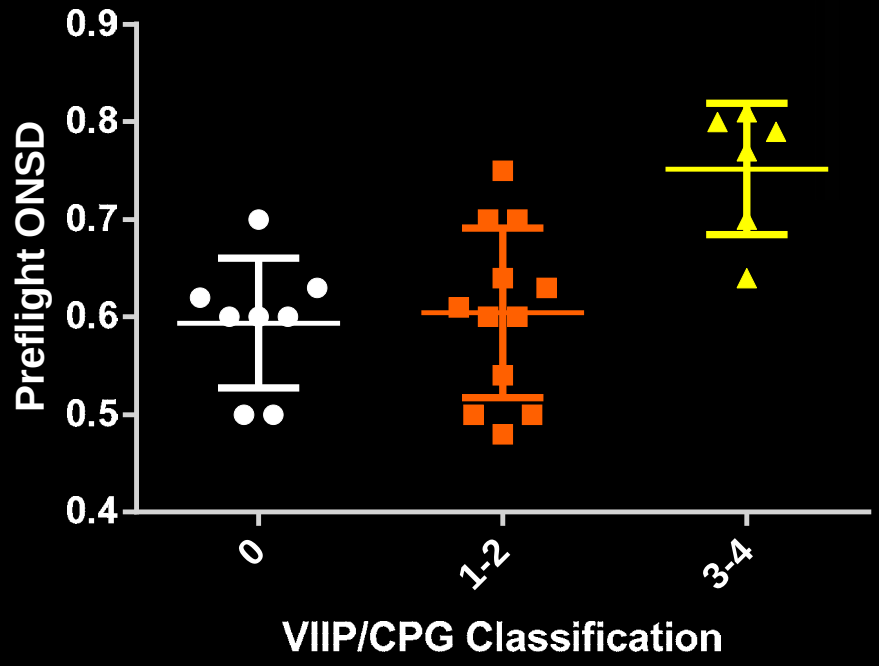
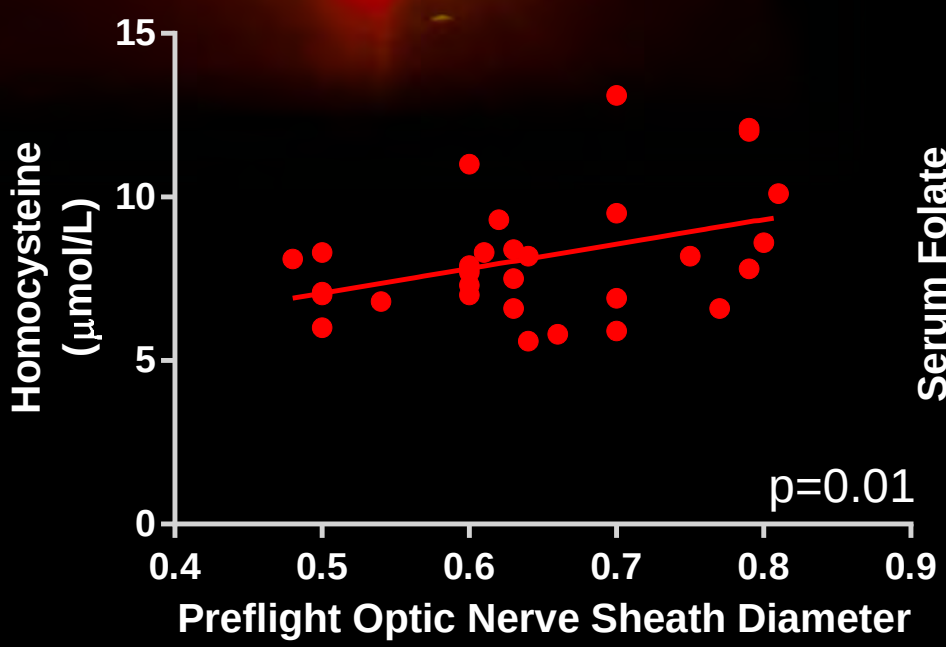
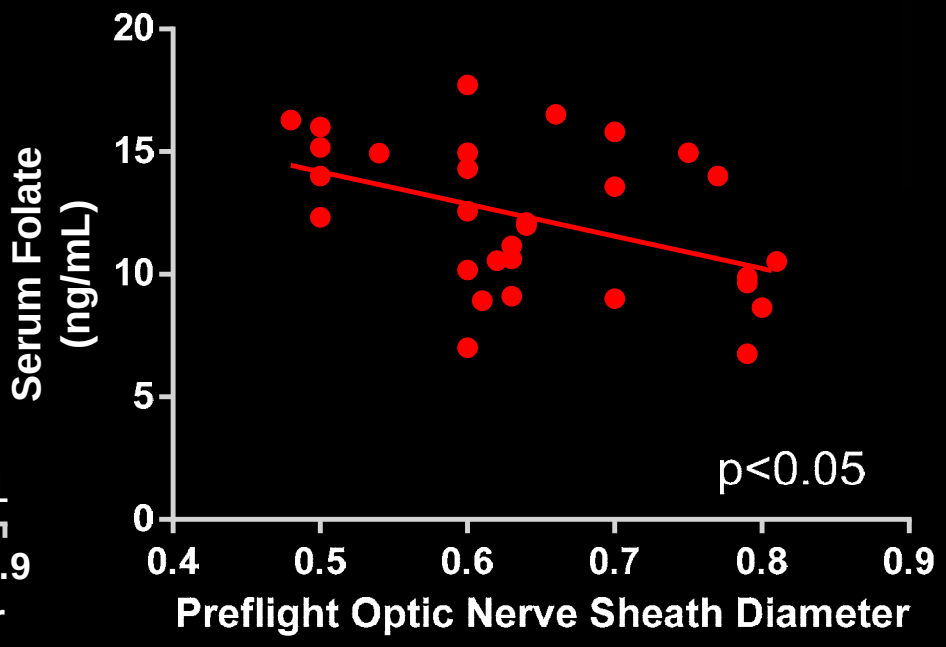
Optic Nerve Sheath Diameter



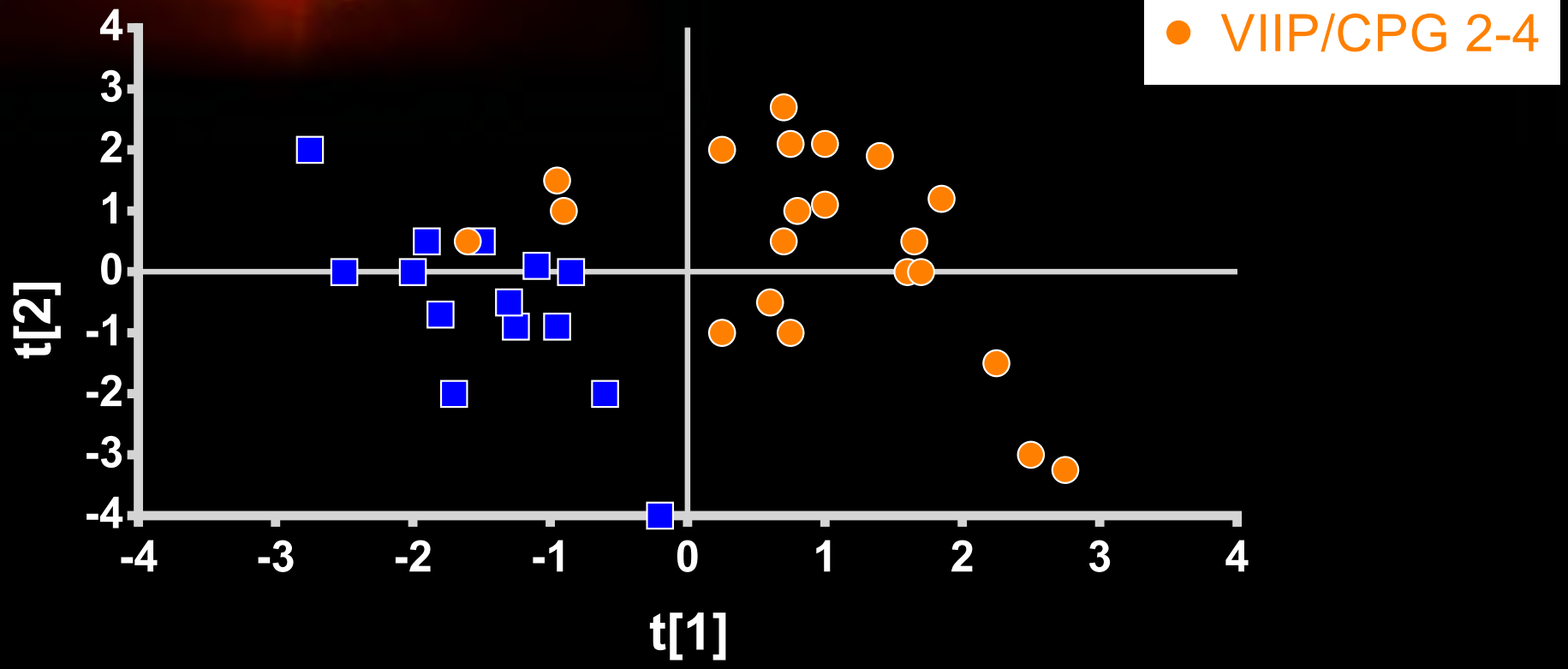


One Carbon: ONSD



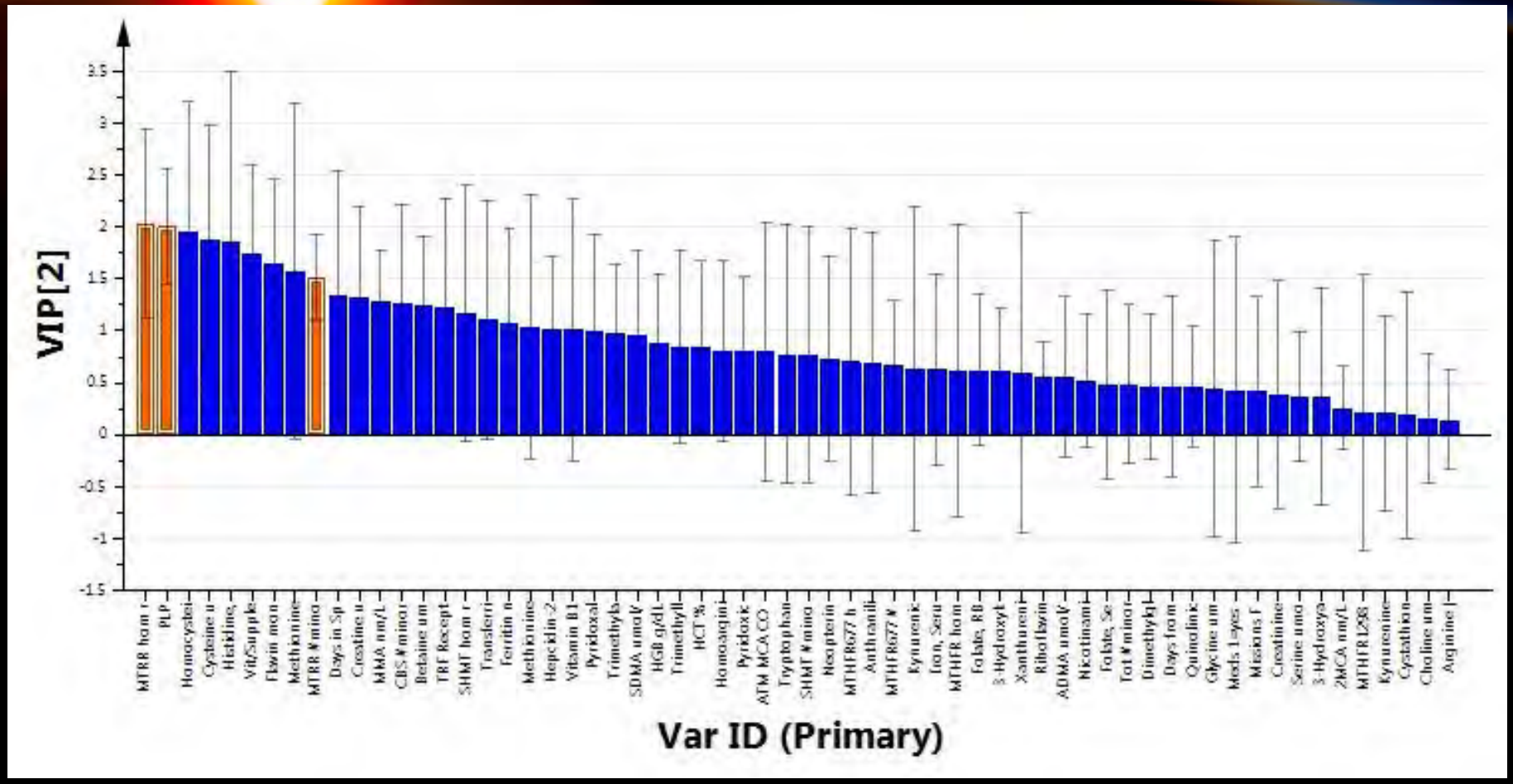


Partial Least Squares Discriminant Analysis



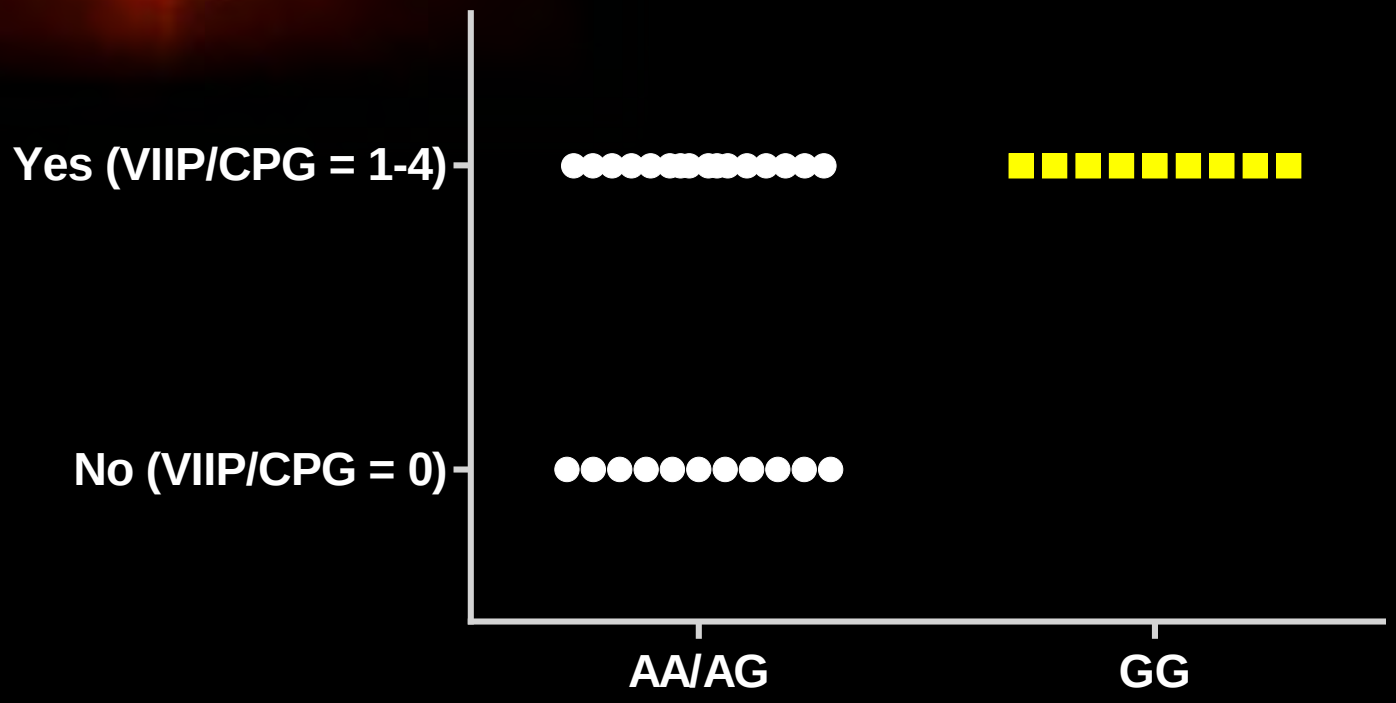
Each dot represents a mathematical function of >30 metabolic measurements for each individual.

Variable Influence in the Projection Plot (VIP)

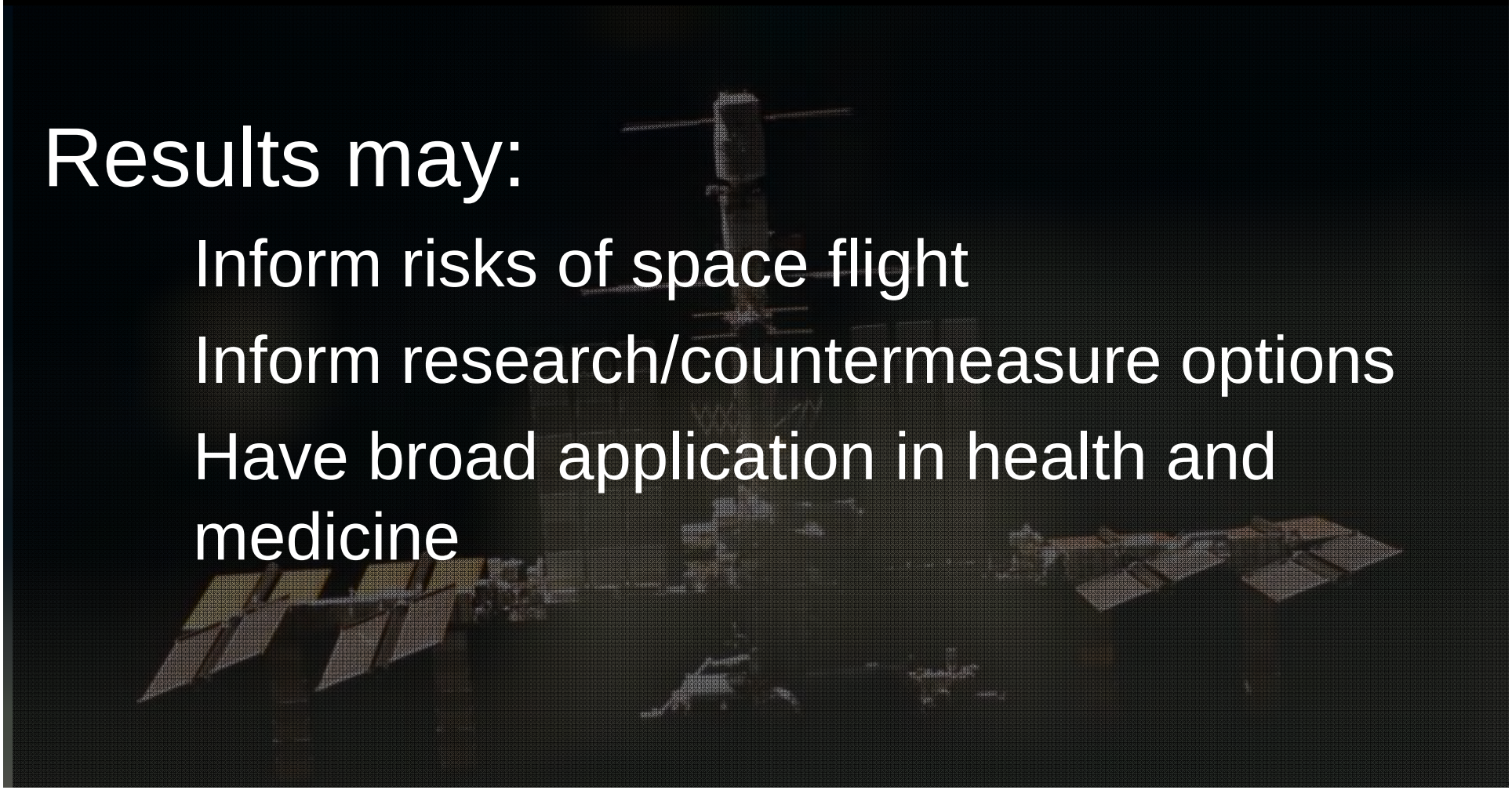


Preliminary discriminating biomarkers: MTRR genotype, PLP

MTRR A66G



Further data and statistical analyses underway…



Results may:

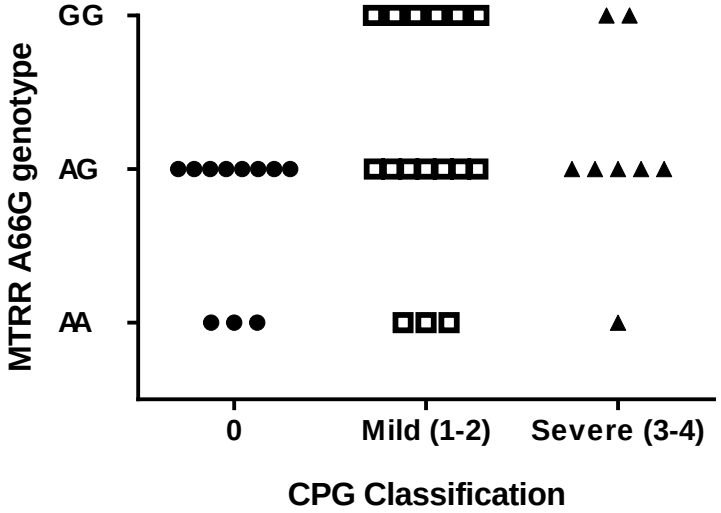
- Inform risks of space flight
- Inform research/countermeasure options
- Have broad application in health and medicine

MTRR/SHMT

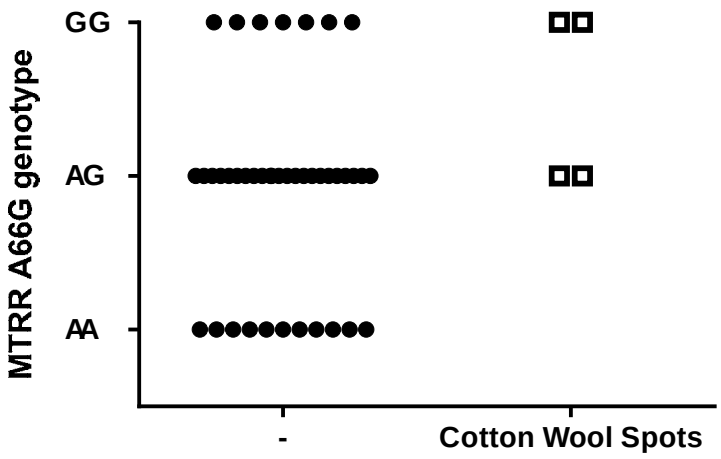
Nutritional Biochemistry Laboratory

JSC/SK3/SM Smith
JSC/SK3/SR Zwart

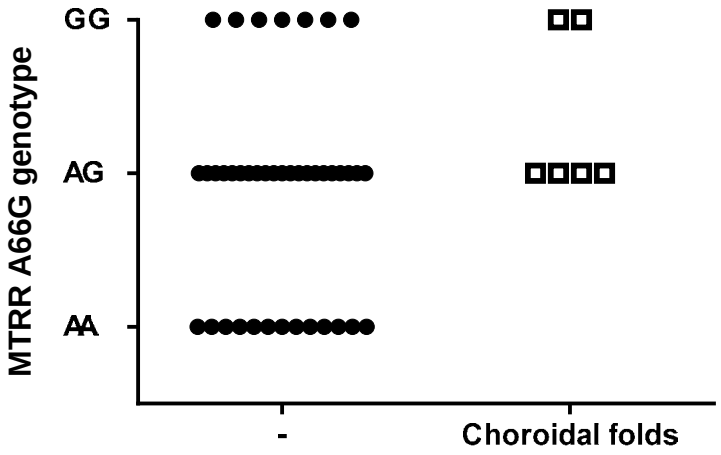
Aug 6, 2014



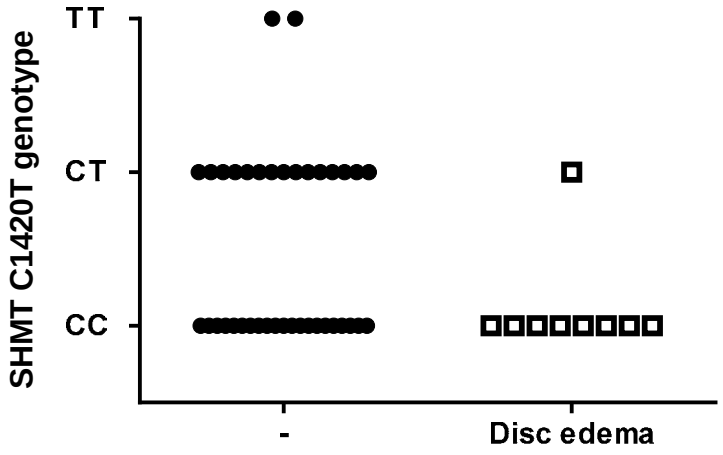
Somers' d: 0.25 (p=0.045)



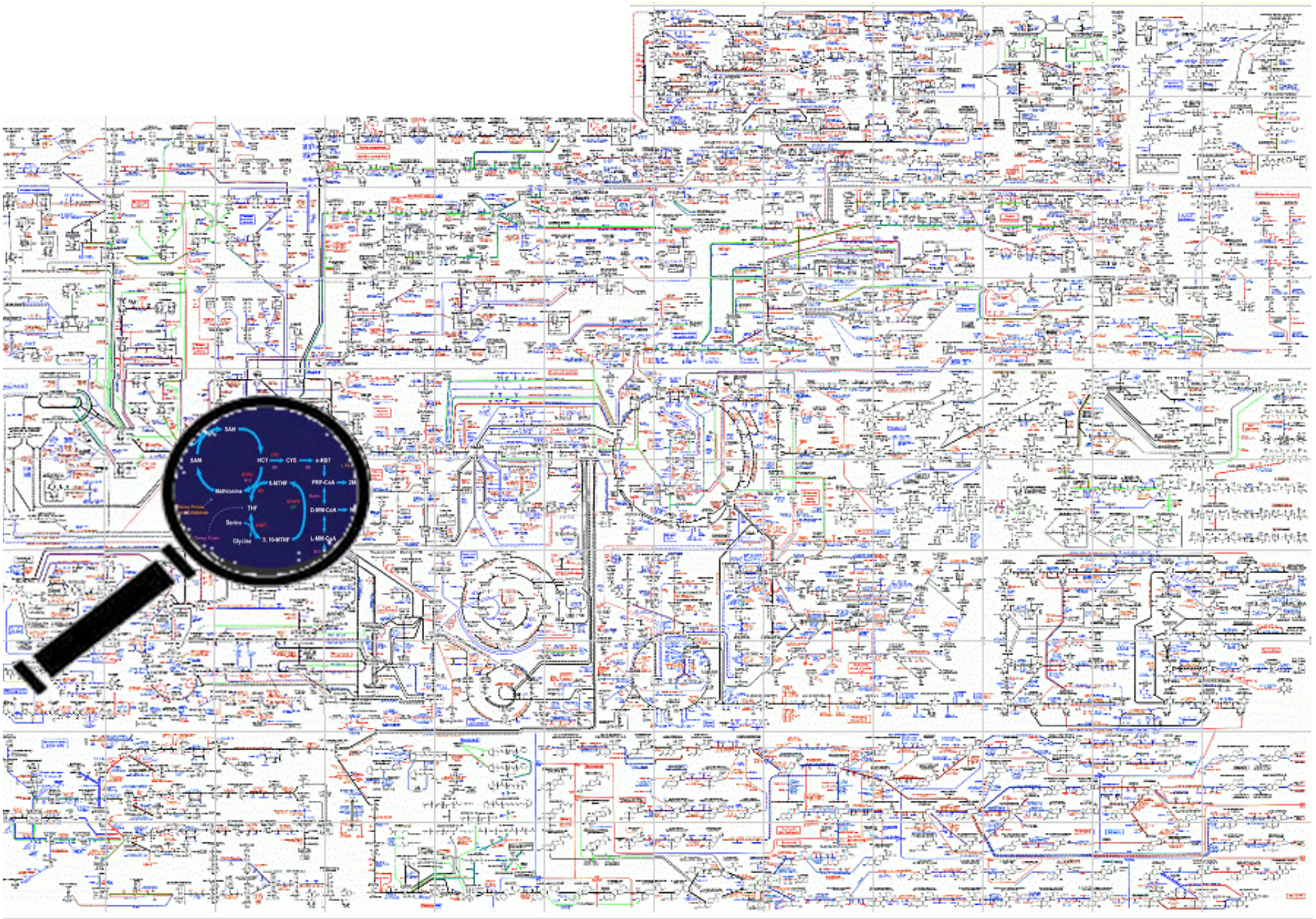
Somers' d: 0.46 (p=0.037)



Somers' d: 0.37 (p=0.03)



Somers' d: -0.34 (p=0.013)


SAH
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α-KBT
5-MTHF
PRP-CoA
Methionine
THF
D-MM-CoA
Serine
Glycine
5, 10-MTHF
L-MM-CoA

Potential Mechanisms and Proposed Forward Work

Nutritional Biochemistry Laboratory

JSC/SK3/SM Smith
JSC/SK3/SR Zwart

Aug 6, 2014

- Mitochondrial dysfunction. Suggestions that this is related to genetic optic neuropathy in the literature, and may explain relationships with changes in iron storage/blood volume/oxidative stress in models of 1C/VIIP data.
  - Expanded 1C metabolomic analyses would help resolve this issue. NOT genetic, just biochemistry.
  - Have query in to Dr. Kundrot as to whether this requires an IRB amendment. *In the consent form, we noted that "Blood will be analyzed in a battery of tests to evaluate intermediates in the one-carbon metabolism pathway, vitamin and iron status, and hematological indices." The protocol, which was updated in November 2012, states "Additionally, we will assay an expanded metabolic profile of one-carbon intermediates involved in folate, vitamin B12 and B6 metabolism. These will be analyzed in the laboratory of Dr. Per Ueland (University of Bergen, Norway). Choline and related metabolites will also be determined." While this still fits the intent of what we are proposing, the one-carbon metabolomics will likely be analyzed in a commercial lab, and not Dr. Ueland's lab. It seems worth noting, we are looking at biochemistry only, and are* ***not*** *proposing any additional genetic testing.*

- Evaluate relationships of blood pressure, IOP, and 1C genetics. Potential for mismatch of pressures causing impaired blood flow, vessel leakage, and pressure on eye.
  - Will submit LSAH request for data.

- Further evaluate 1C (and related) genetics.
  - Potential that the MTRR is not causal, and is simply associated with another gene in the same haplotype. An initial evaluation of ancestry could help clarify.
    - Will submit IRB request.

MTRR A66G Incidence

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JSC/SK3/SR Zwart

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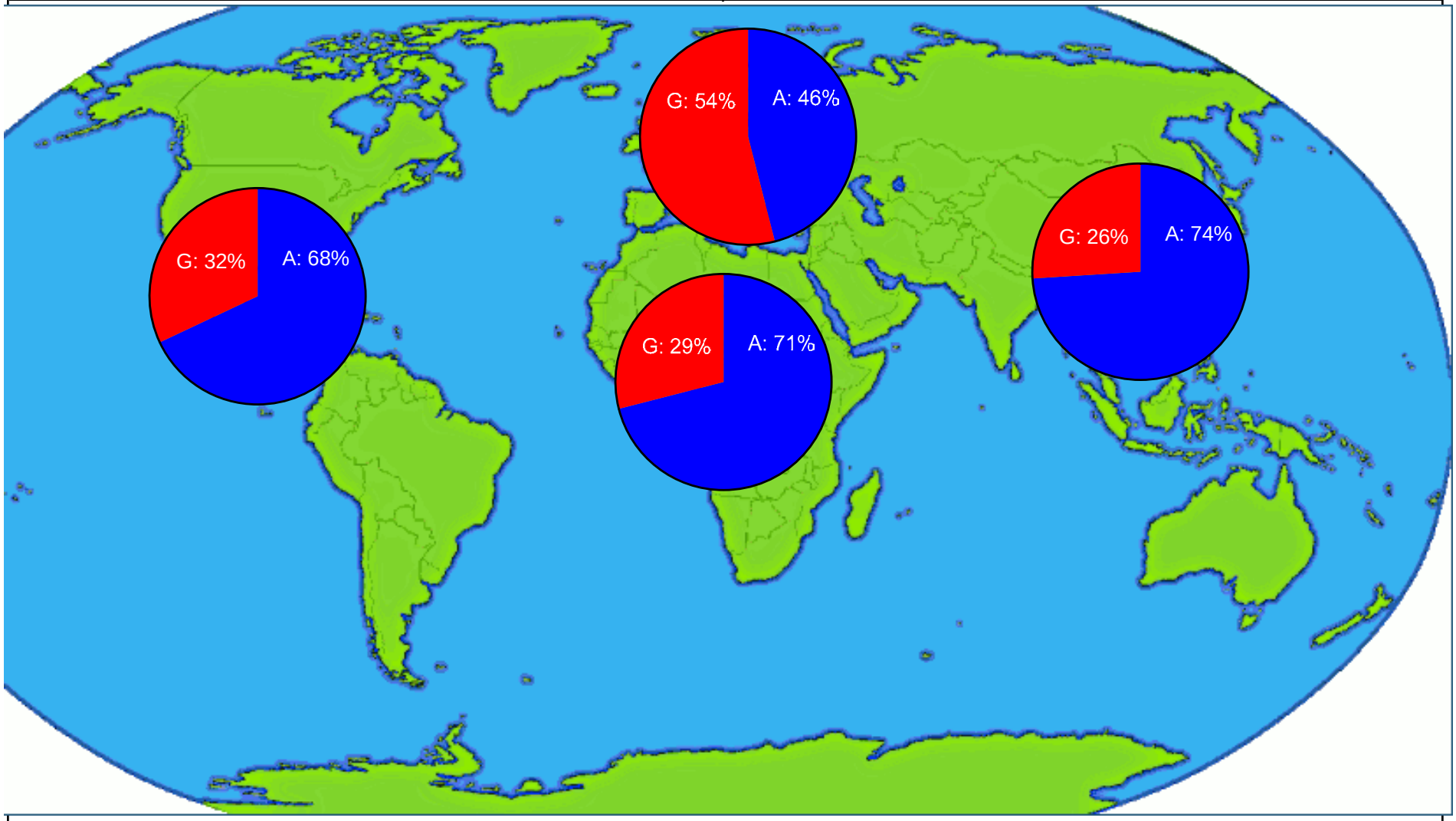
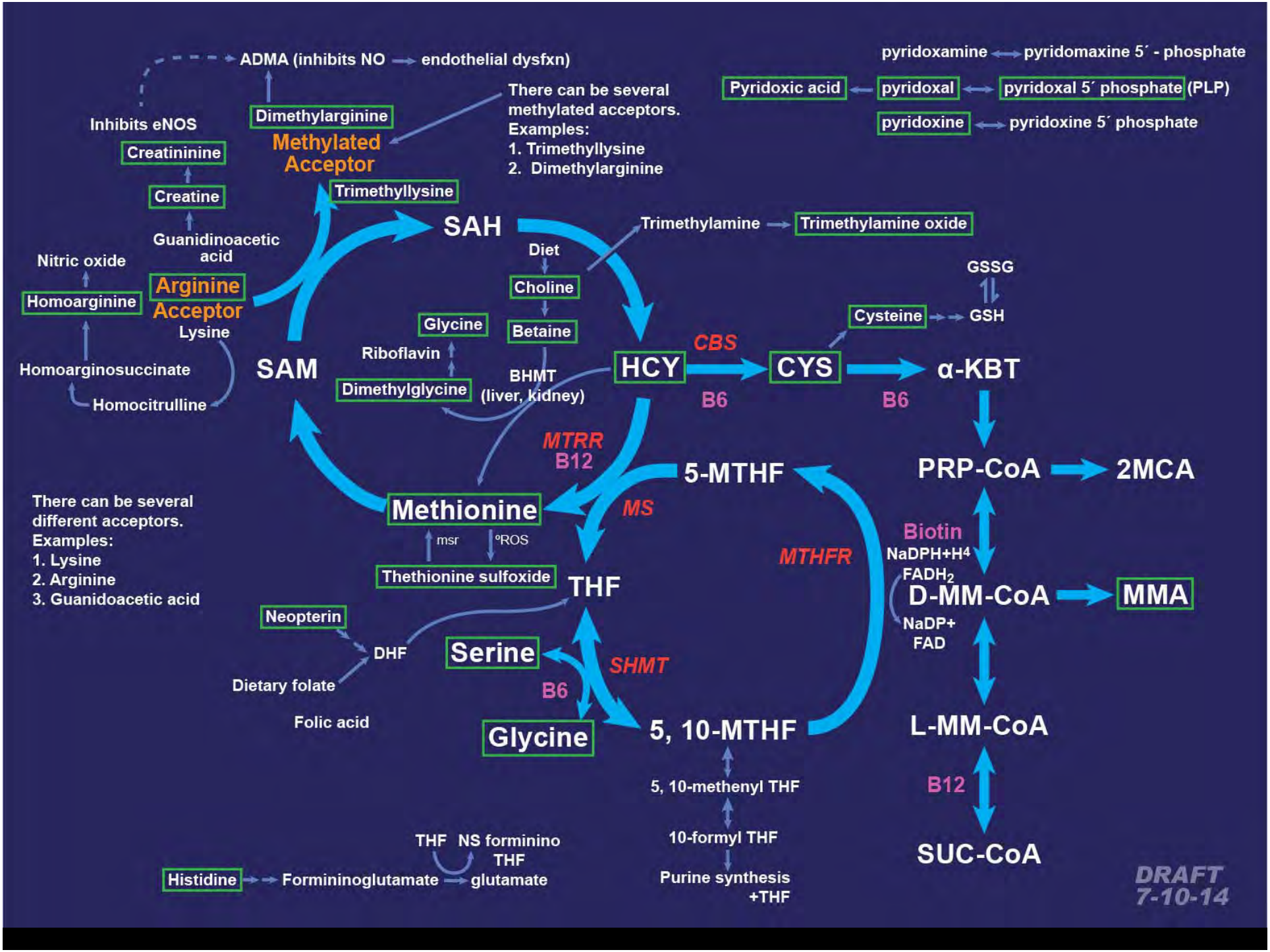
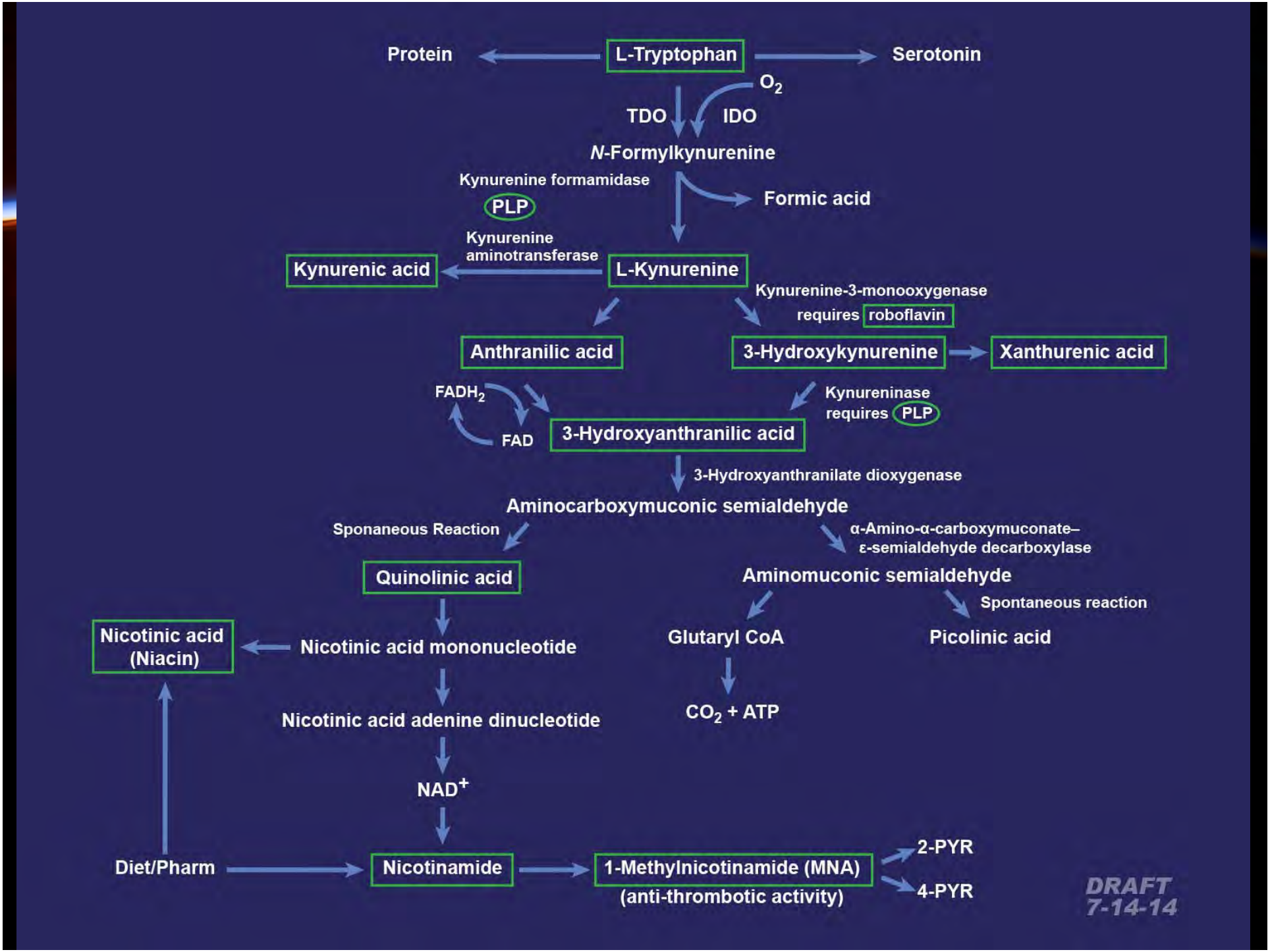


- Utah residents w/ Northern European background: A: 43%, G: 57%
- Finland: A: 38%, G: 62%
- Italy (Toscani): A: 60%, G: 40%

- Further evaluate 1C (and related) genetics.
  - We measured 5 polymorphisms, taking a very conservative approach to the initial genetic analysis. We propose to evaluate a wide range of one-carbon related genes (19 genes, and 35 polymorphisms).
    - Will submit proposal to HRP

- Amendment currently submitted to IRB (on 8/19 agenda).
  - Extend 1C study subject recruitment:
    - Crewmembers not previously briefed
    - Crewmembers from last 3 Shuttle flights, where more intensive eye exams were conducted.
  - This will help with the number of crewmembers with no flight experience
- CB MMM update/status presentation scheduled for August 25.


ADMA (inhibits NO → endothelial dysfxn)
Inhibits eNOS
Dimethylarginine
Methylated Acceptor
There can be several methylated acceptors.
Examples:
1. Trimethyllysine
2. Dimethylarginine
Creatininine
Creatine
Guanidinoacetic acid
Trimethyllysine
SAH
Trimethylamine → Trimethylamine oxide
Nitric oxide
Homoarginine
Arginine Acceptor
Lysine
Diet
Choline
Betaine
Glycine
Riboflavin
Dimethylglycine
BHMT (liver, kidney)
Homoarginosuccinate
Homocitrulline
SAM
HCY
CBS
B6
CYS
Cysteine
GSSG
GSH
B6
α-KBT
MTRR B12
5-MTHF
MS
Methionine
msr
°ROS
Thethionine sulfoxide
THF
MTHFR
There can be several different acceptors.
Examples:
1. Lysine
2. Arginine
3. Guanidoacetic acid
Neopterin
DHF
Dietary folate
Folic acid
Serine
SHMT
B6
Glycine
5, 10-MTHF
5, 10-methenyl THF
10-formyl THF
Purine synthesis +THF
Histidine → Formininoglutamate
THF
NS forminino THF
glutamate
PRP-CoA → 2MCA
Biotin
NaDPH+H4
FADH2
D-MM-CoA → MMA
NaDP+
FAD
L-MM-CoA
B12
SUC-CoA
pyridoxamine ↔ pyridomaxine 5´ - phosphate
Pyridoxic acid ← pyridoxal ↔ pyridoxal 5´ phosphate (PLP)
pyridoxine ↔ pyridoxine 5´ phosphate
DRAFT
7-10-14


Protein
L-Tryptophan
Serotonin
O_2
TDO
IDO
N-Formylkynurenine
Kynurenine formamidase
PLP
Formic acid
Kynurenine aminotransferase
Kynurenic acid
L-Kynurenine
Kynurenine-3-monooxygenase
requires roboflavin
Anthranilic acid
3-Hydroxykynurenine
Xanthurenic acid
$FADH_2$
FAD
Kynureninase
requires PLP
3-Hydroxyanthranilic acid
3-Hydroxyanthranilate dioxygenase
Aminocarboxymuconic semialdehyde
Sponaneous Reaction
α-Amino-α-carboxymuconate–
ε-semialdehyde decarboxylase
Quinolinic acid
Aminomuconic semialdehyde
Spontaneous reaction
Nicotinic acid
(Niacin)
Nicotinic acid mononucleotide
Glutaryl CoA
Picolinic acid
CO_2 + ATP
Nicotinic acid adenine dinucleotide
NAD^+
Diet/Pharm
Nicotinamide
1-Methylnicotinamide (MNA)
(anti-thrombotic activity)
2-PYR
4-PYR
DRAFT
7-14-14