Gene-guided Nutrition Interventions

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Steven Zeisel Disclosures

AFFILIATION/FINANCIAL INTERESTS	CORPORATE ORGANIZATION
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Scientific Advisory Board/Consultant:	Metabolon, CFEN, SNPitty, Enzymotec, Ingenuity Foods, Second Science
Speakers' Support/Honorarium:	Balchem, Nutrapharma
Stock Shareholder:	Zthera
Other Financial or Material Support/Honorarium:	None

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Gene-guided medical foods

www.zthera.com

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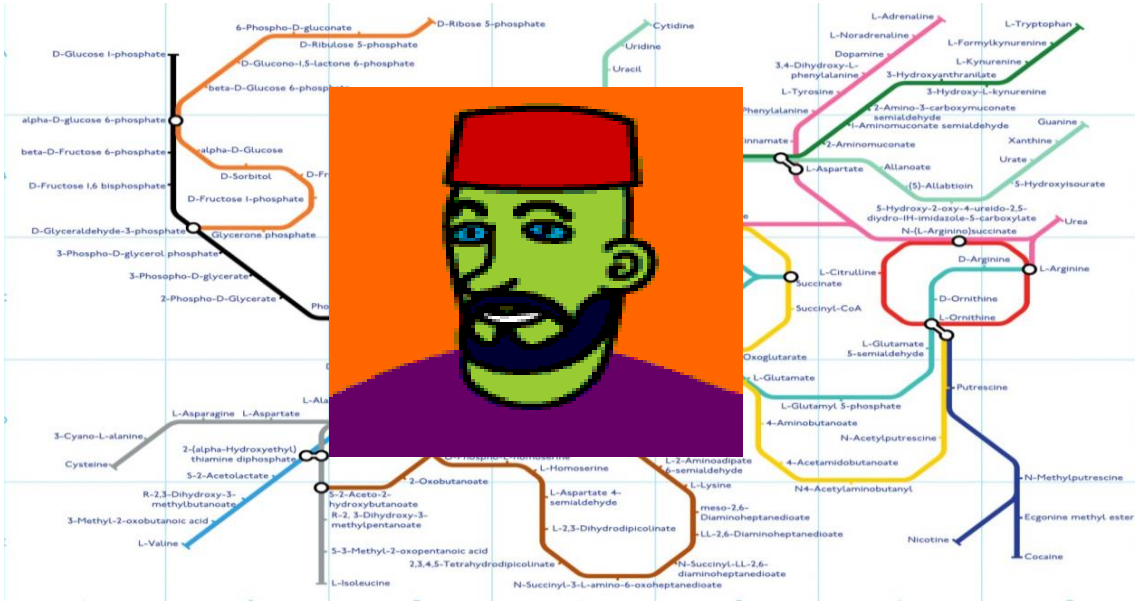
Modern science tells us that people are metabolically different



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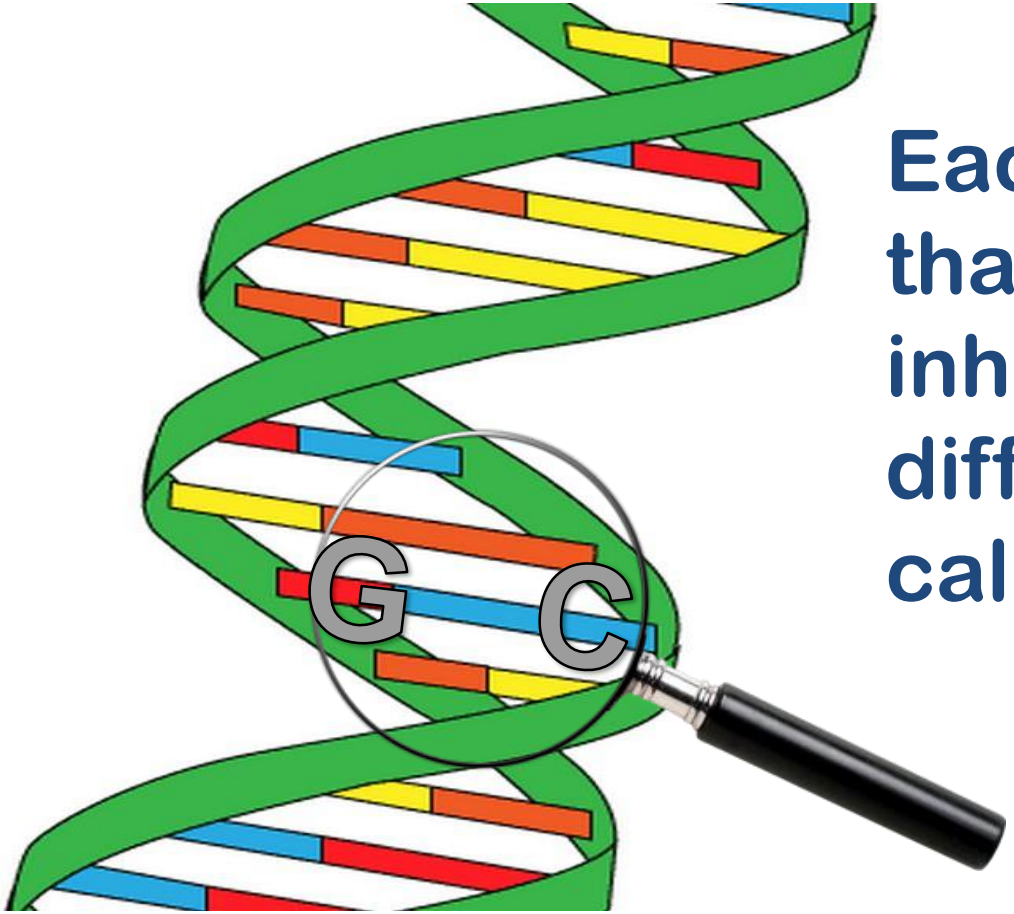

Each of us has more than 50,000 common, inherited “spelling” differences in our genes called SNPs.

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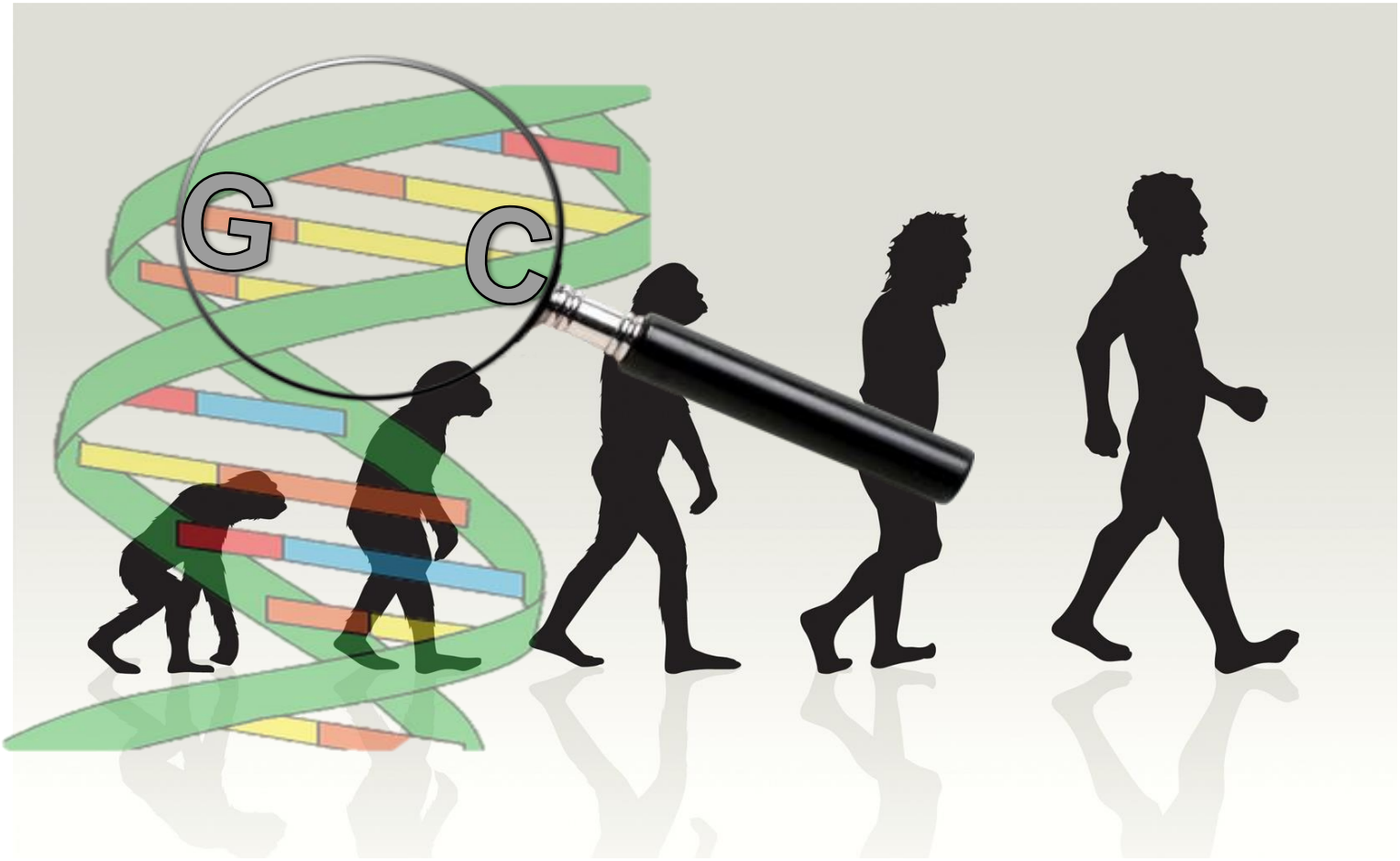
We inherited them from our ancestors.



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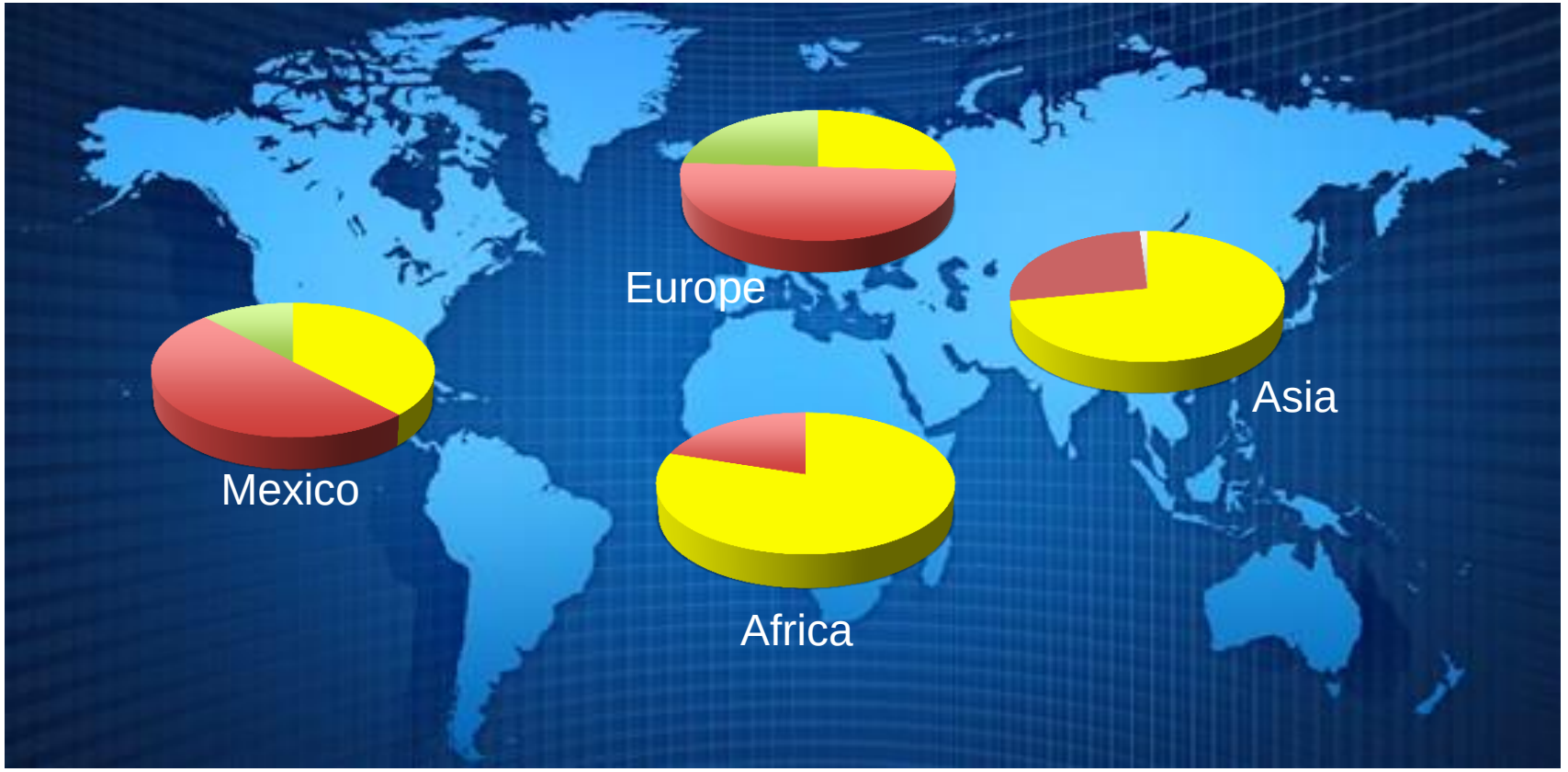
Populations differ in distribution of many SNPS



GG GC CC

Need more choline

rs12325817 *PEMT* G→C

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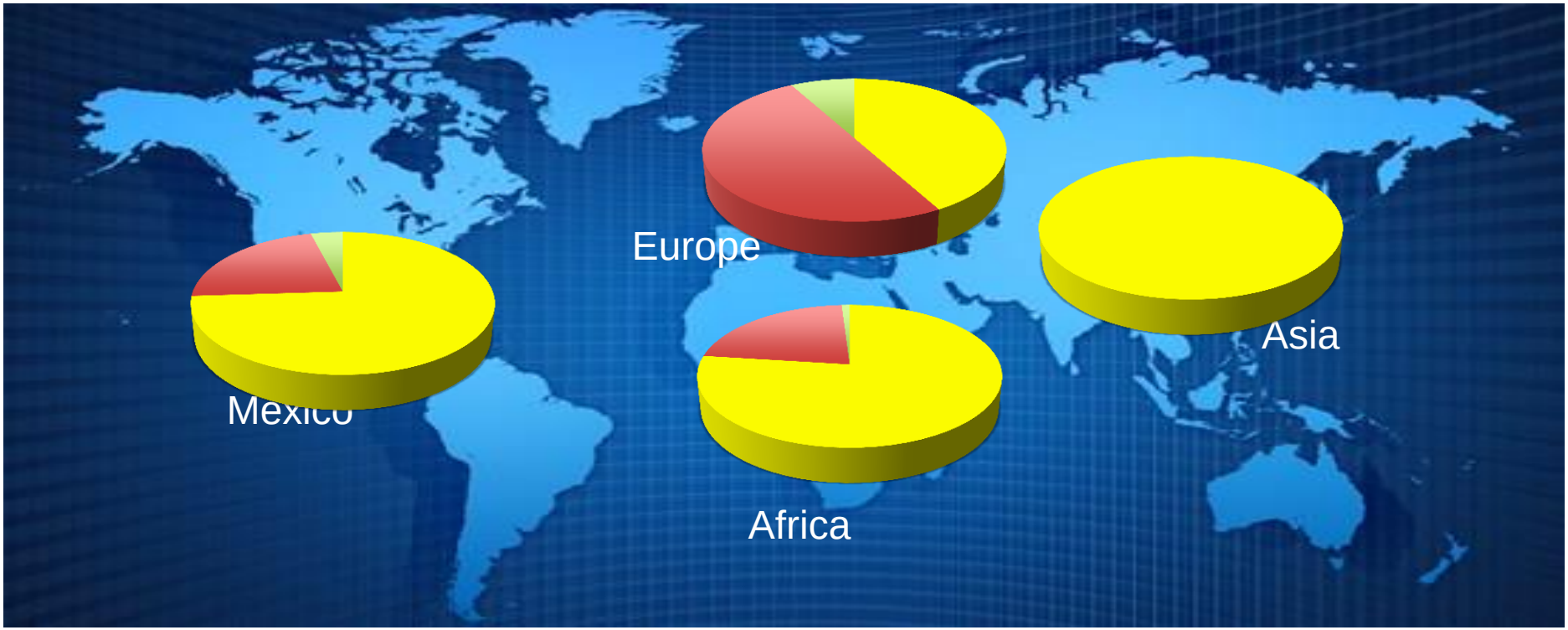
Populations differ in distribution of many SNPS



Populations differ in distribution of many SNPS

Normal nutrition is composed of many metabolic pathways that nutrients must transit.

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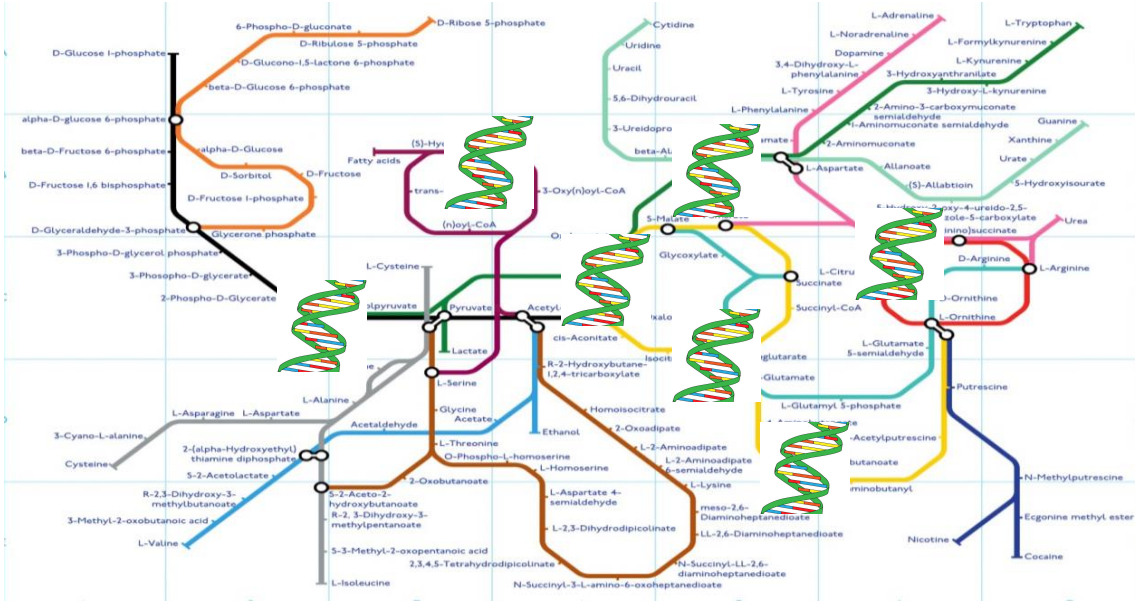
Each of these pathways depends on many genes.



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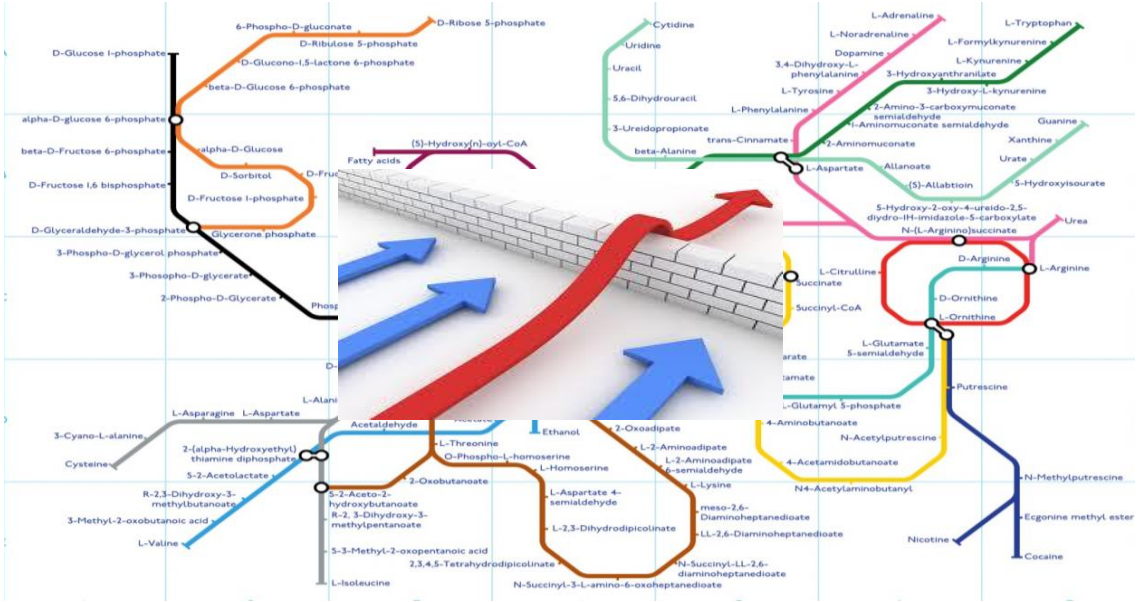
When these genes are polymorphic (alternatively "spelled"; SNPs), roadblocks in metabolism can occur



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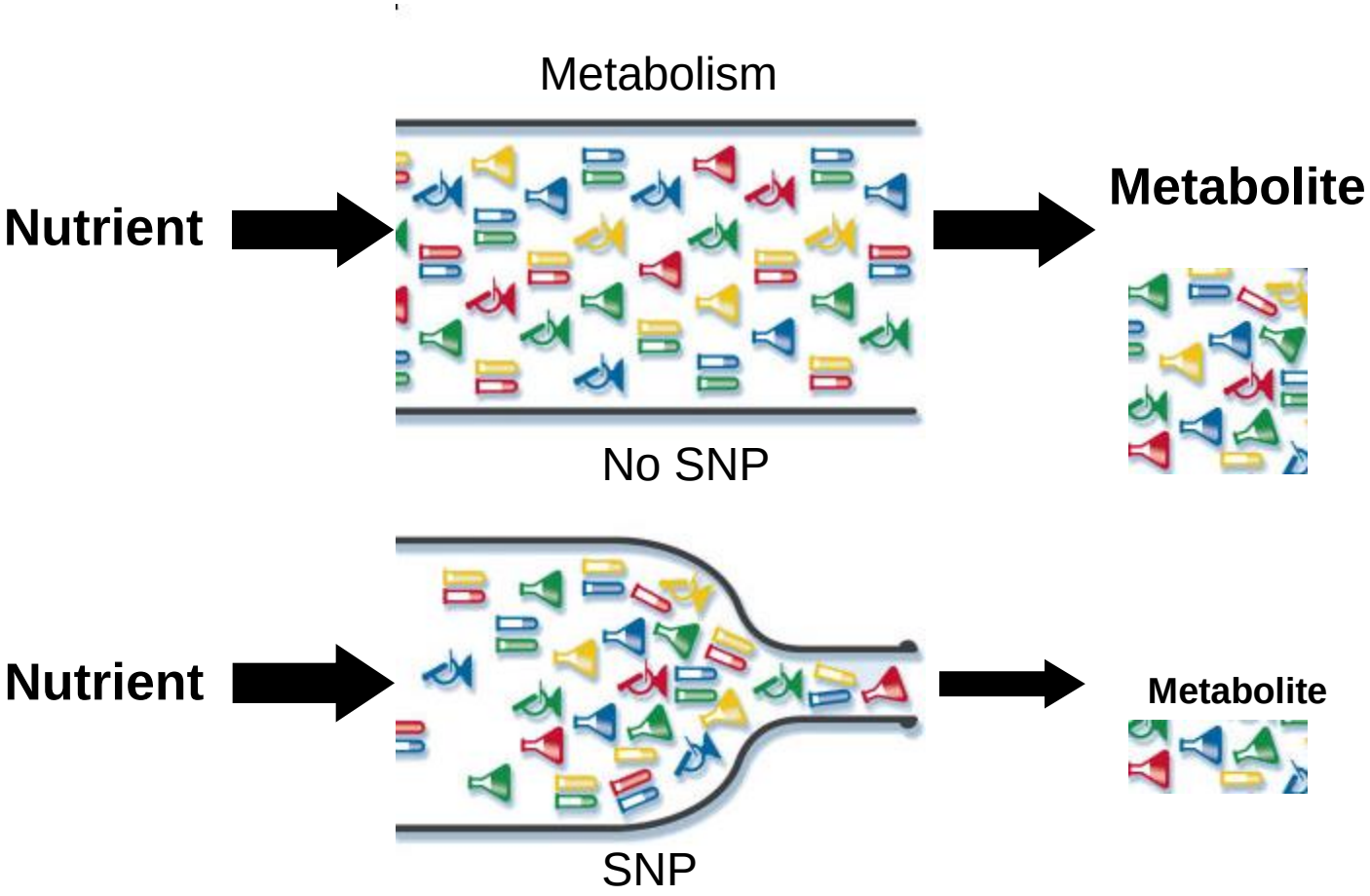
These genetic roadblocks can make metabolism inefficient



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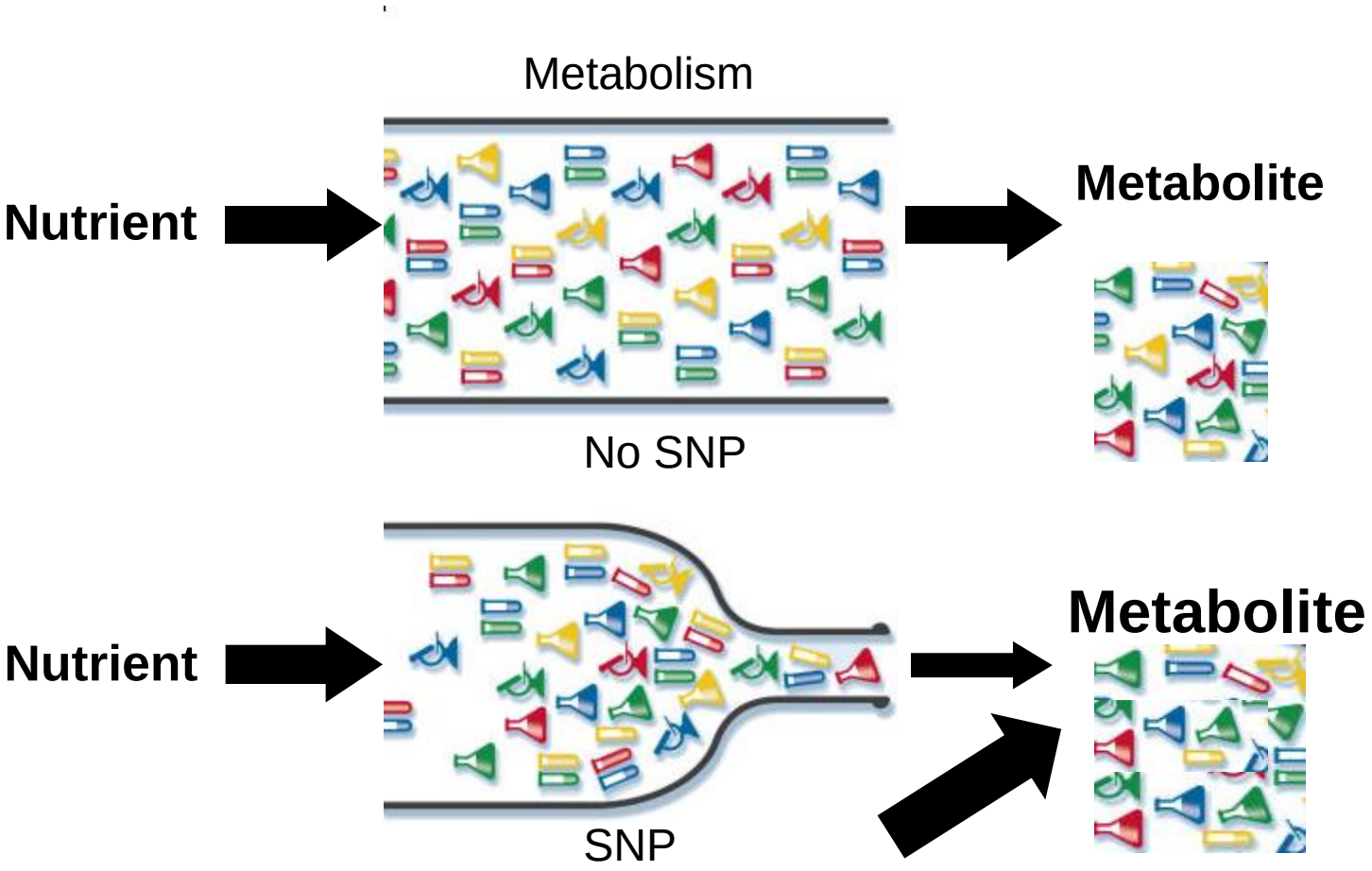
Diet may bypass roadblock caused by SNP



DIET DELIVERS METABOLITE

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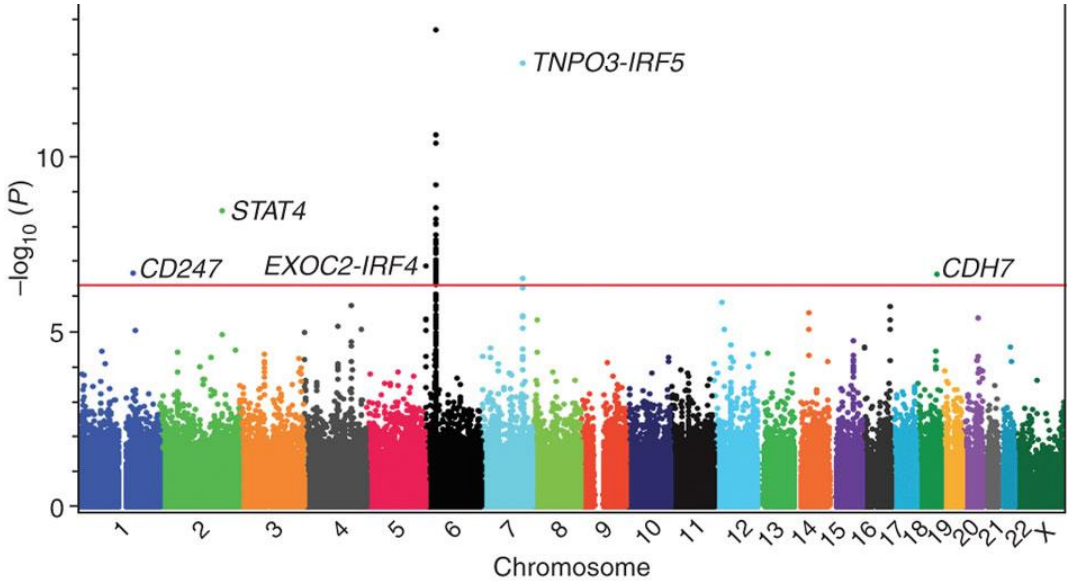
Diet intake is often missing in GWAS studies



Thus, GWAS studies miss important nutrition SNPS because high-diet nonresponders cancel out low-diet responders.

Need to look at people challenged by low or high intake.

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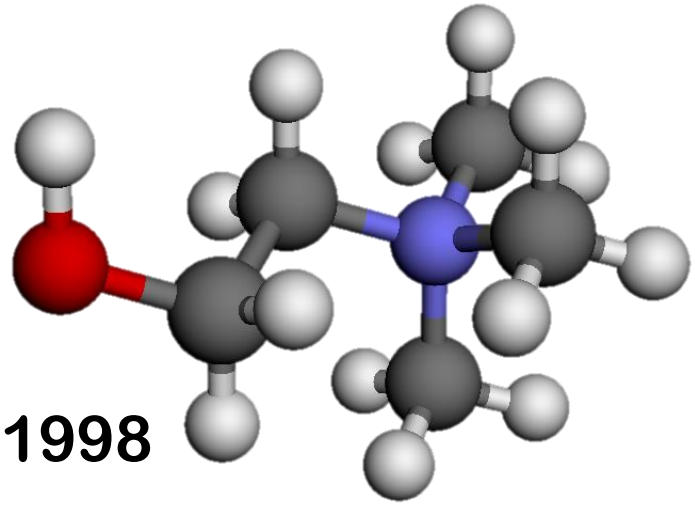
Our work on expanding the catalog of metabolically important SNPs



CHOLINE

- IOM AI diet recommendation 1998
- FDA DRI 2016, good source labeling
- AMA 2016 recommends inclusion in prenatals
- Important for liver and muscle
- Critical for fetal development
- Human requirements vary by genotype

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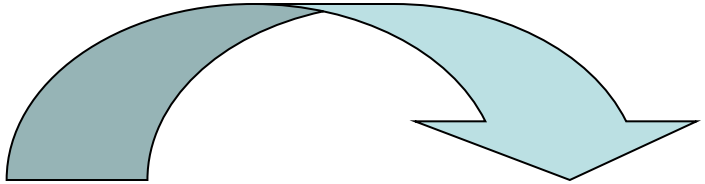
Endogenous synthesis of choline

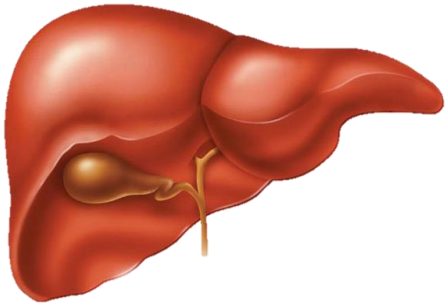
Phosphatidylethanolamine – *N*- methyltransferase

(PEMT)



***3 S*-adenosylmethionine + phosphatidylethanolamine**

phosphatidylcholine



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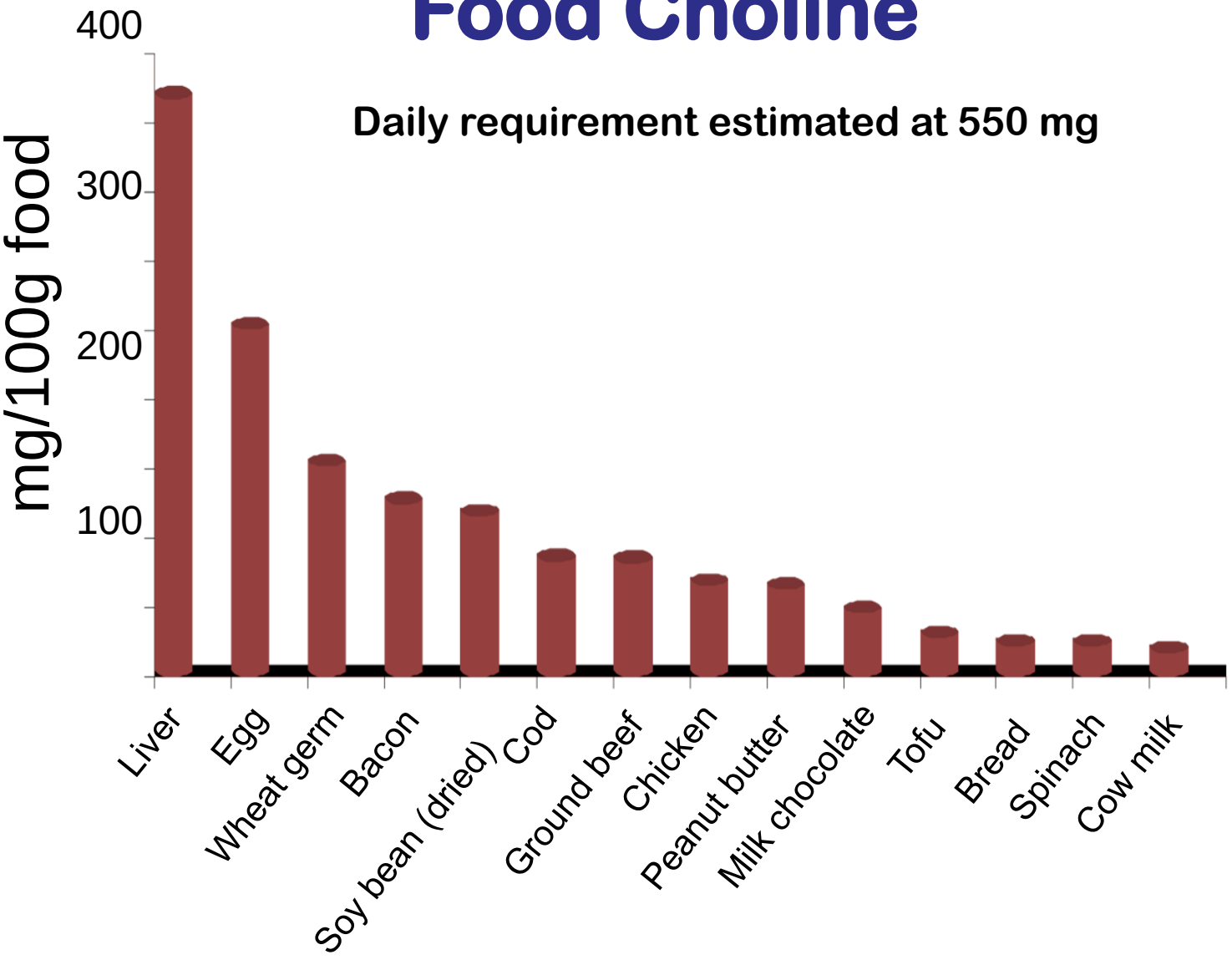
Food Choline



From http://www.ars.usda.gov/Services/docs.htm?docid=6232

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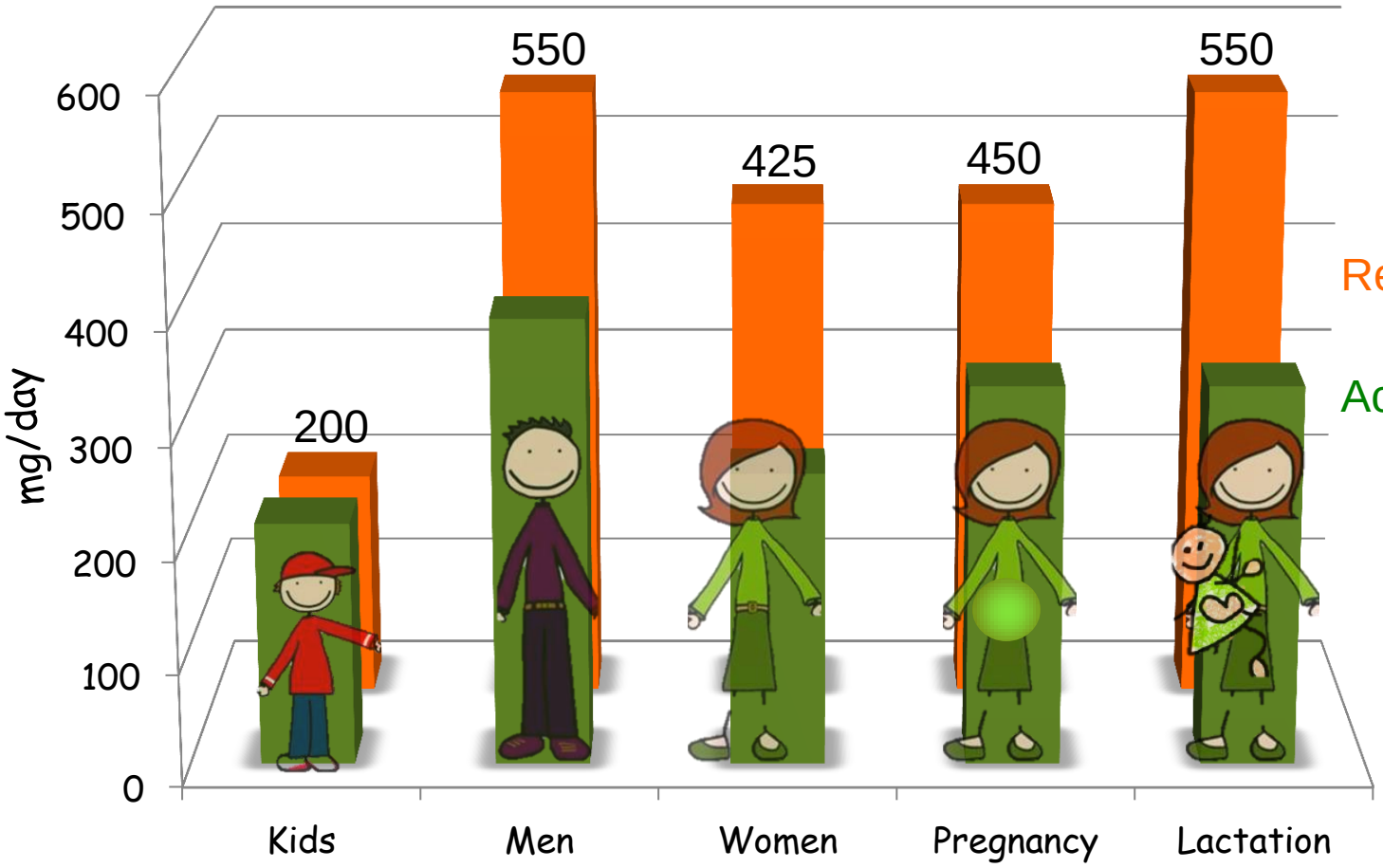
Most Americans do not achieve Adequate Intake for choline.



Recommended (AI)

Actual Intake

NHANES 2009-2014

from http://cholinecouncil.com/health_professional/

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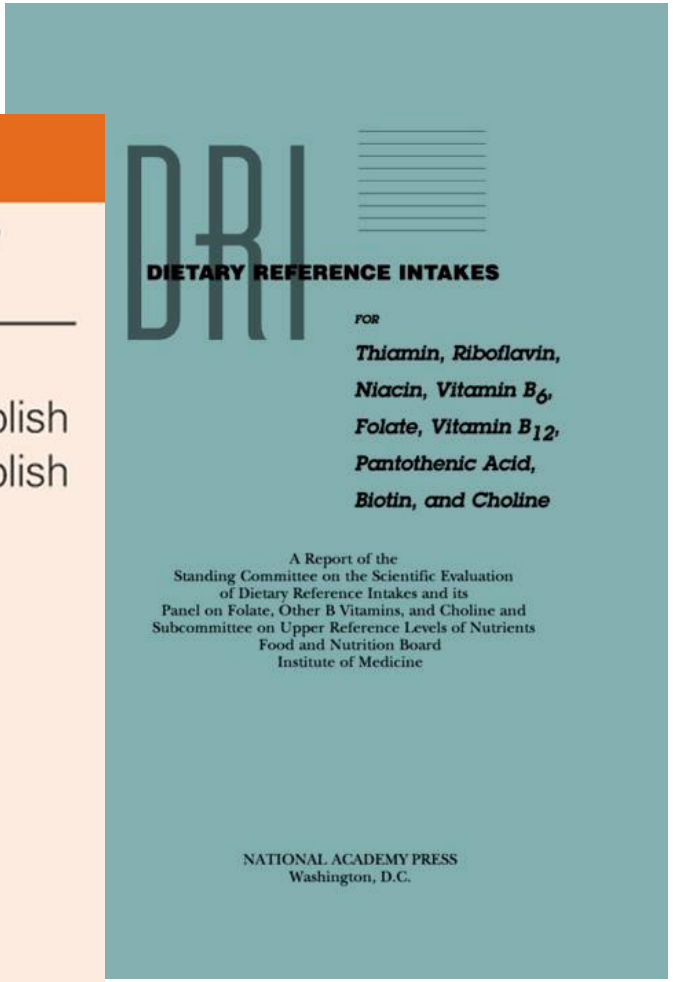
US Recommendations for choline

Population and Age	Adequate Intake	Tolerable Upper Limit (UL)
Infants, mo		
0–6	125 mg/d, 18 mg/kg	Not possible to establish
6–12	150 mg/d	Not possible to establish
Children, y		
1–3	200 mg/d	1,000 mg/d
4–8	250 mg/d	1,000 mg/d
9–13	375 mg/d	2,000 mg/d
Men, y		
14–18	550 mg/d	3,000 mg/d
≥19	550 mg/d	3,500 mg/d
Women, y		
14–18	400 mg/d	3,000 mg/d
≥19	425 mg/d	3,500 mg/d
Pregnant	450 mg/d	Age-appropriate UL
Lactating	550 mg/d	Age-appropriate UL

Data from the Institute of Medicine, National Academy of Sciences.[11]



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Most humans required dietary choline

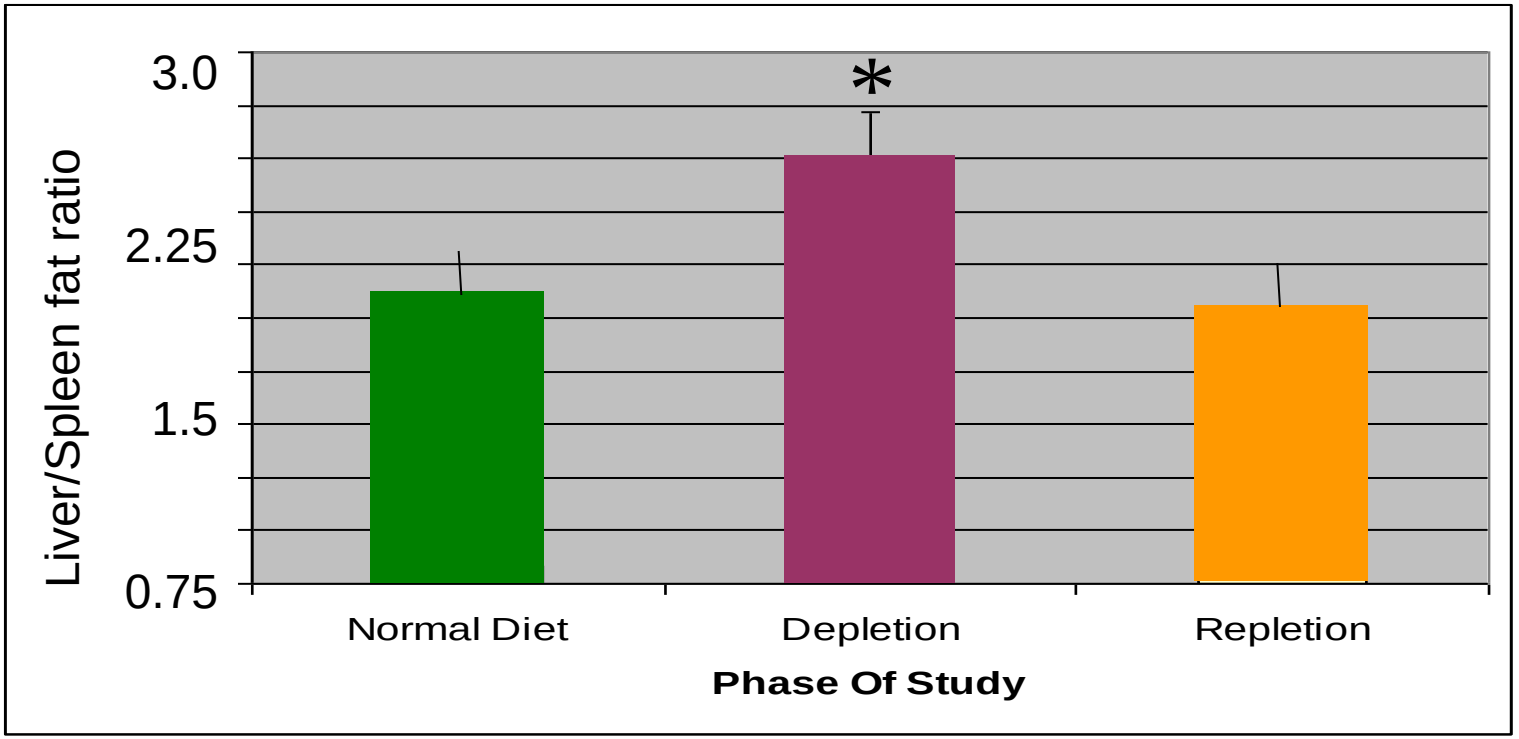
Dietary requirement differs by gender

77% 80% 44%

developed fatty liver, liver damage or muscle damage associated with choline deficiency.

American Journal of Clinical Nutrition 85(5):1275-85 , 2007

Liver fat increases



American Journal of Clinical Nutrition 85(5):1275-85 , 2007

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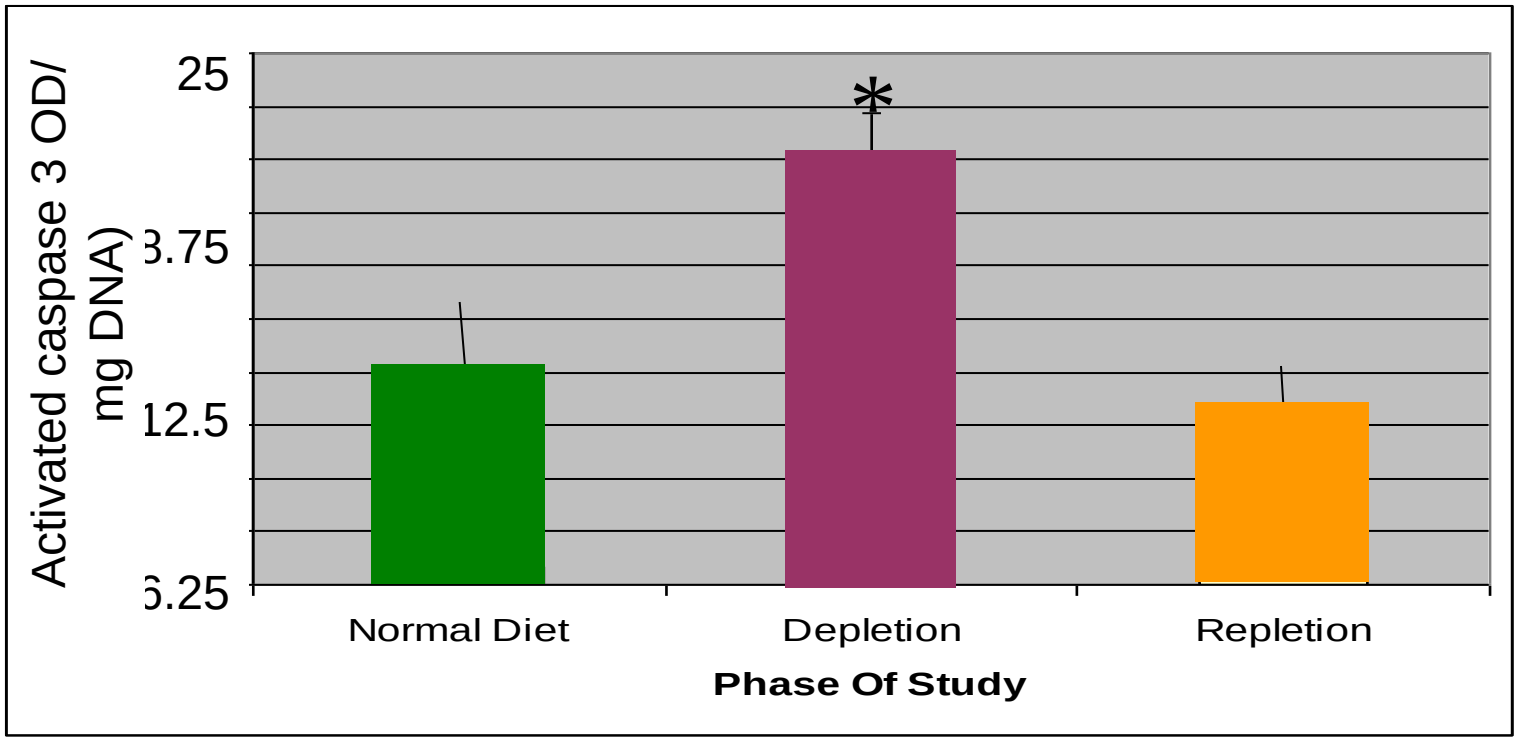
Cell suicide (apoptosis) activated in lymphocytes



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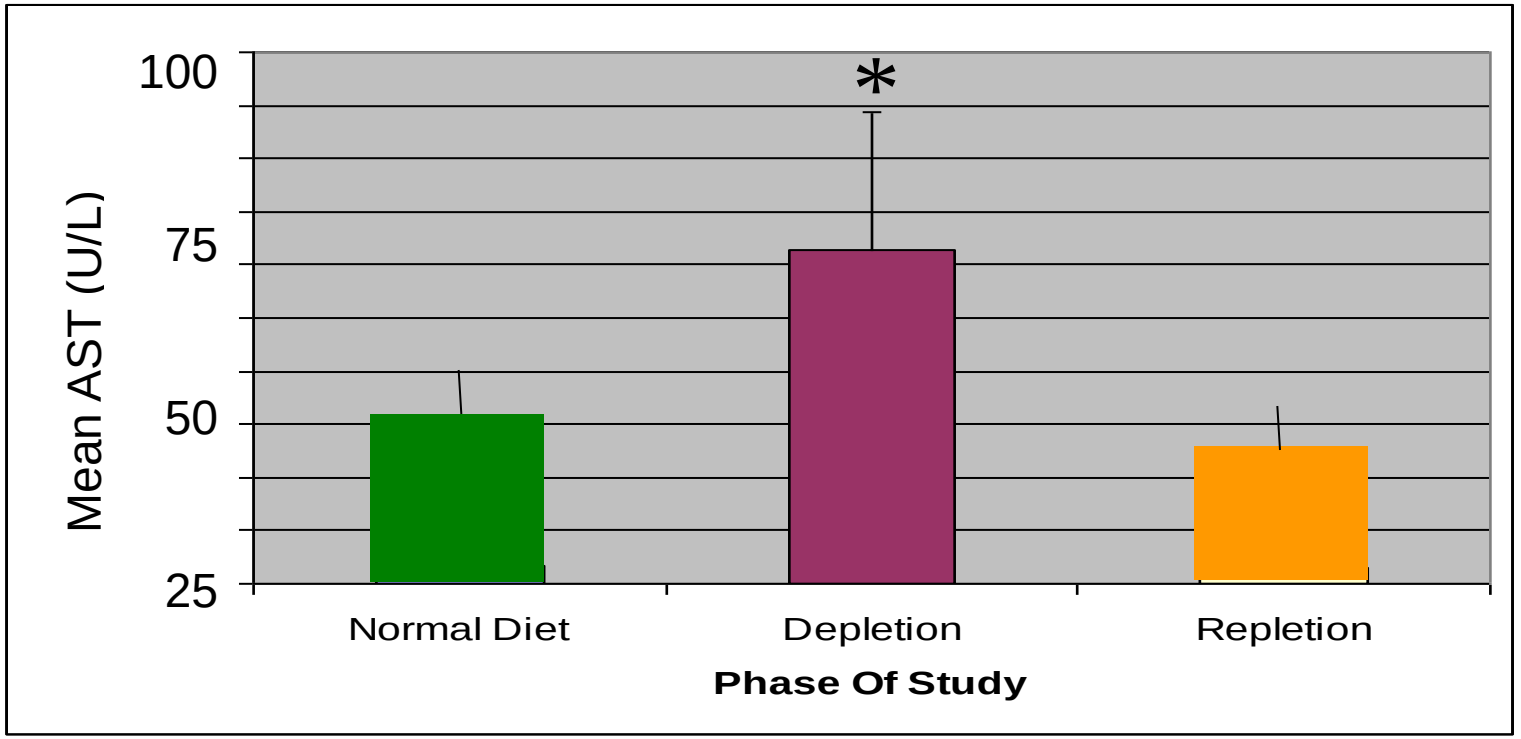
Liver cells damaged



American Journal of Clinical Nutrition 85(5):1275-85 , 2007

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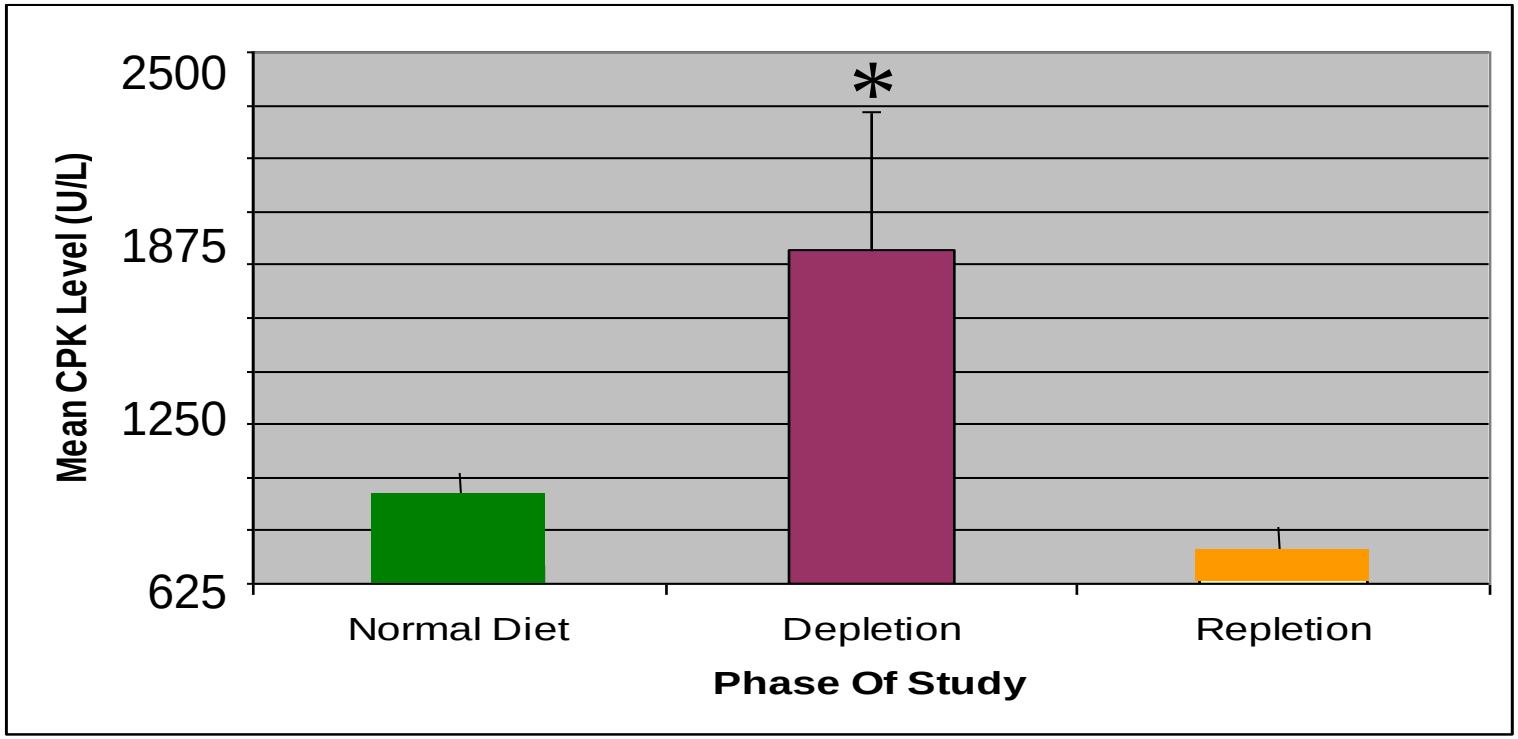
Muscle cells damaged



American Journal of Clinical Nutrition 85(5):1275-85, 2007

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Why do some premenopausal women require less dietary choline?

23% 20% 56%

Did <u>not</u> need to eat choline for 42 days.

American Journal of Clinical Nutrition 85(5):1275-85 , 2007

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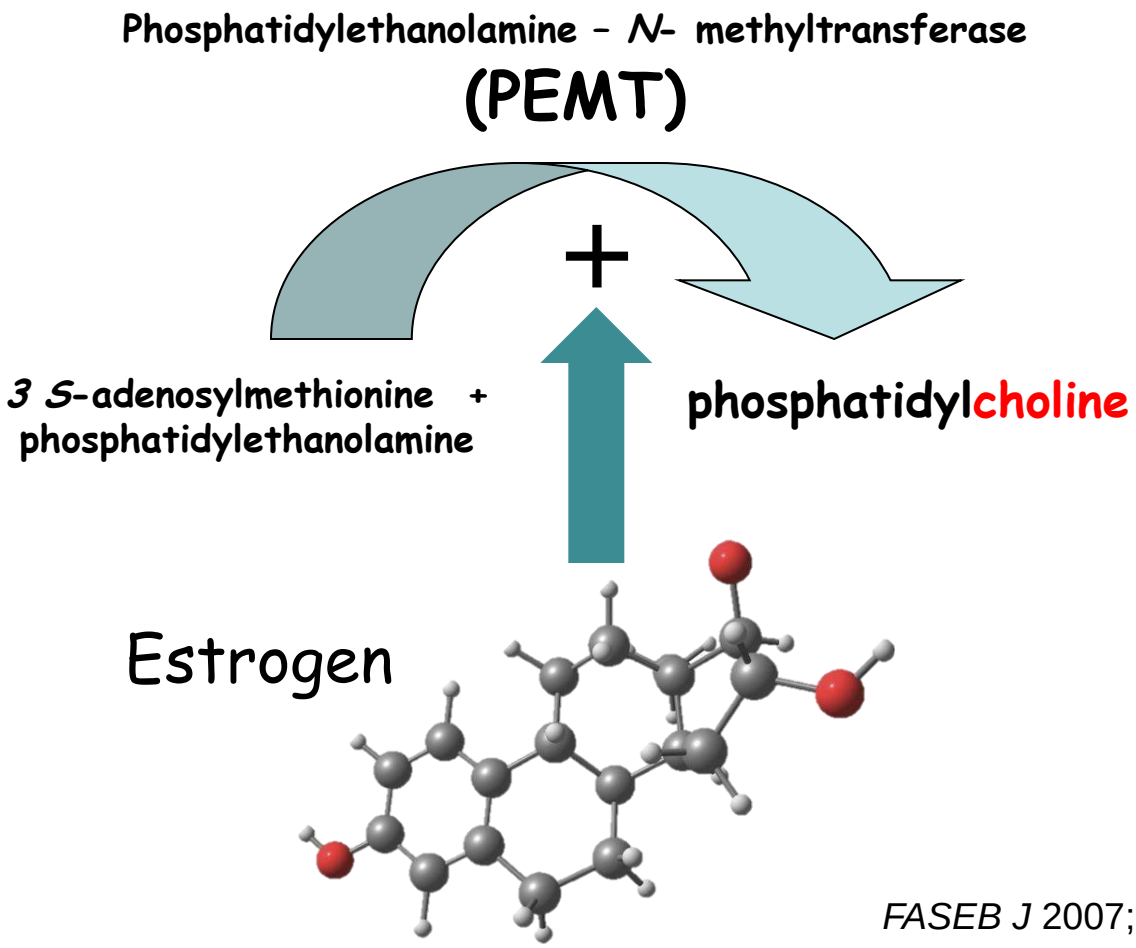
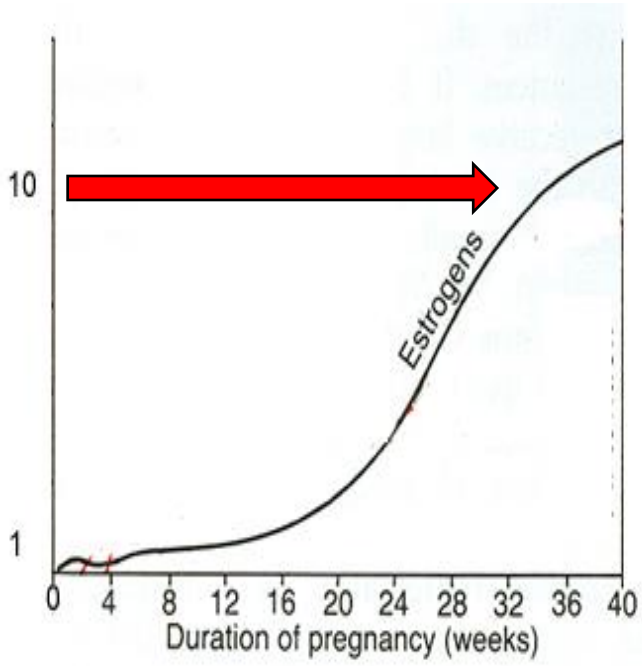
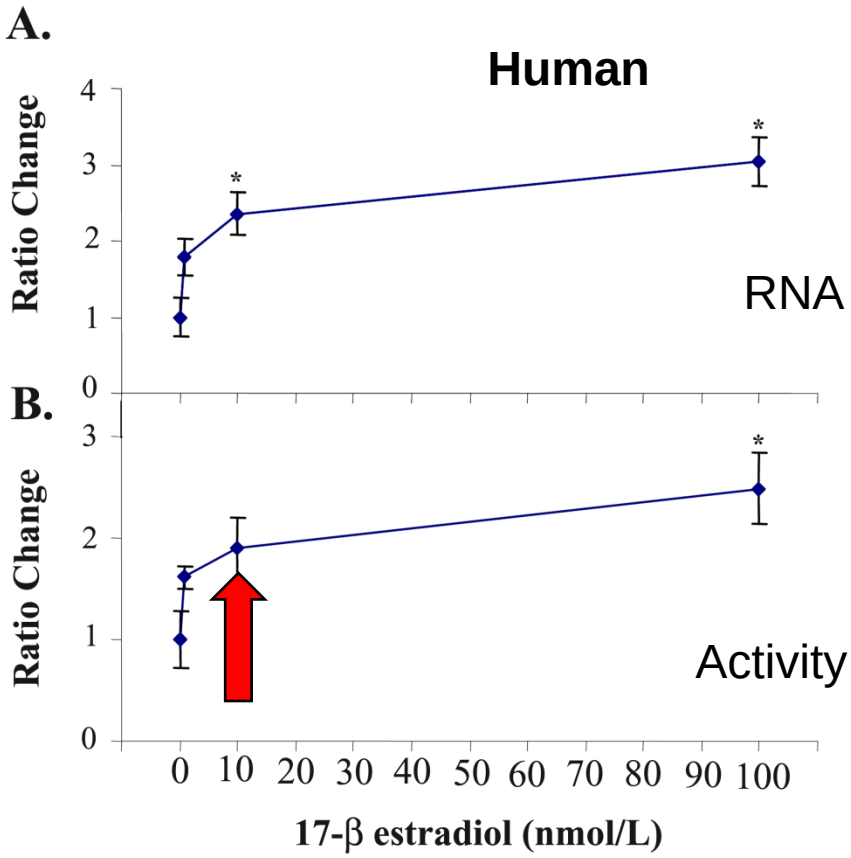
Endogenous synthesis of choline induced by estrogen



FASEB J 2007;21:2622-2632

PEMT induced by estrogen





FASEB J 2007;21:2622-2632

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Why do some premenopausal women still need dietary choline?

44%

need to eat choline or they develop fatty liver and liver damage.

American Journal of Clinical Nutrition 85(5):1275-85 , 2007

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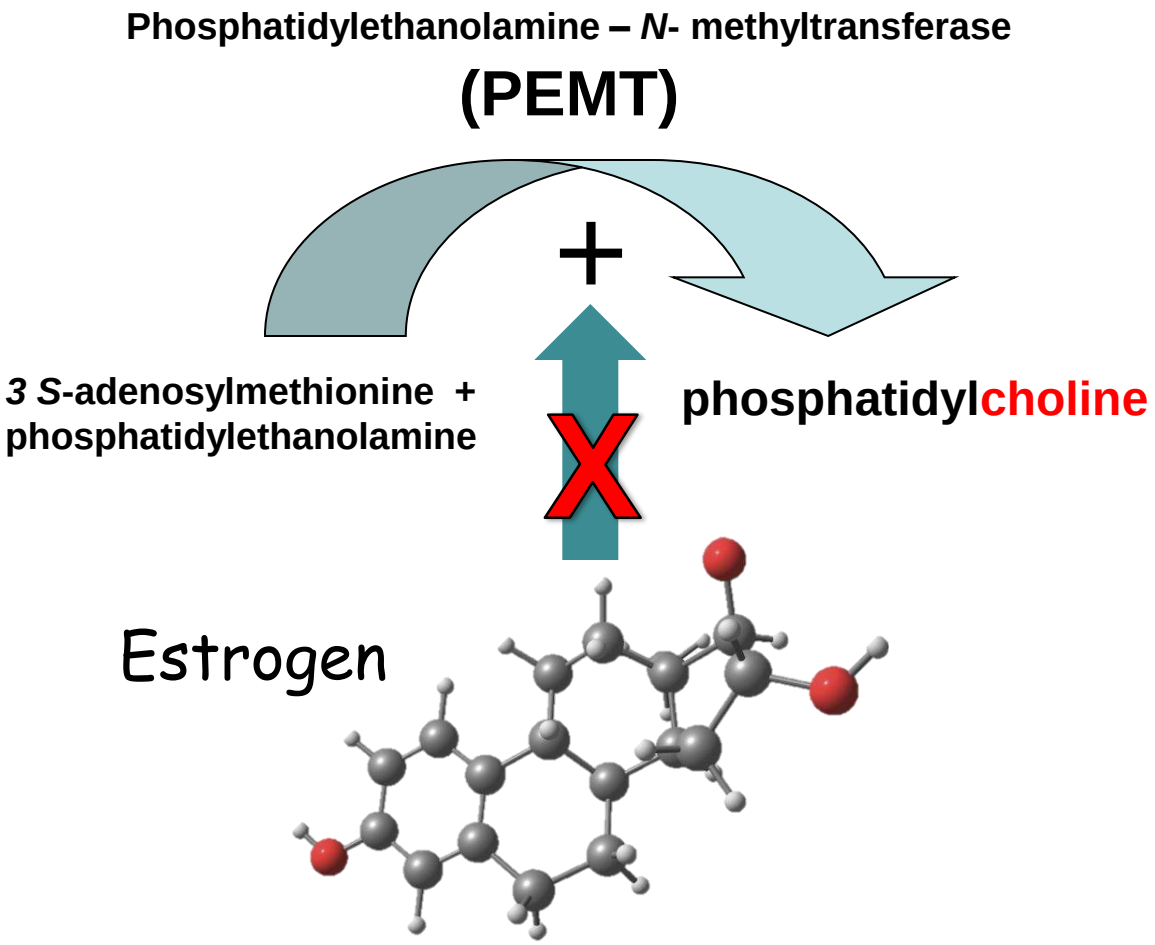
PEMT SNP rs12325817 prevents induction by estrogen



J. Biol. Chem. 2011;286:1649-1658

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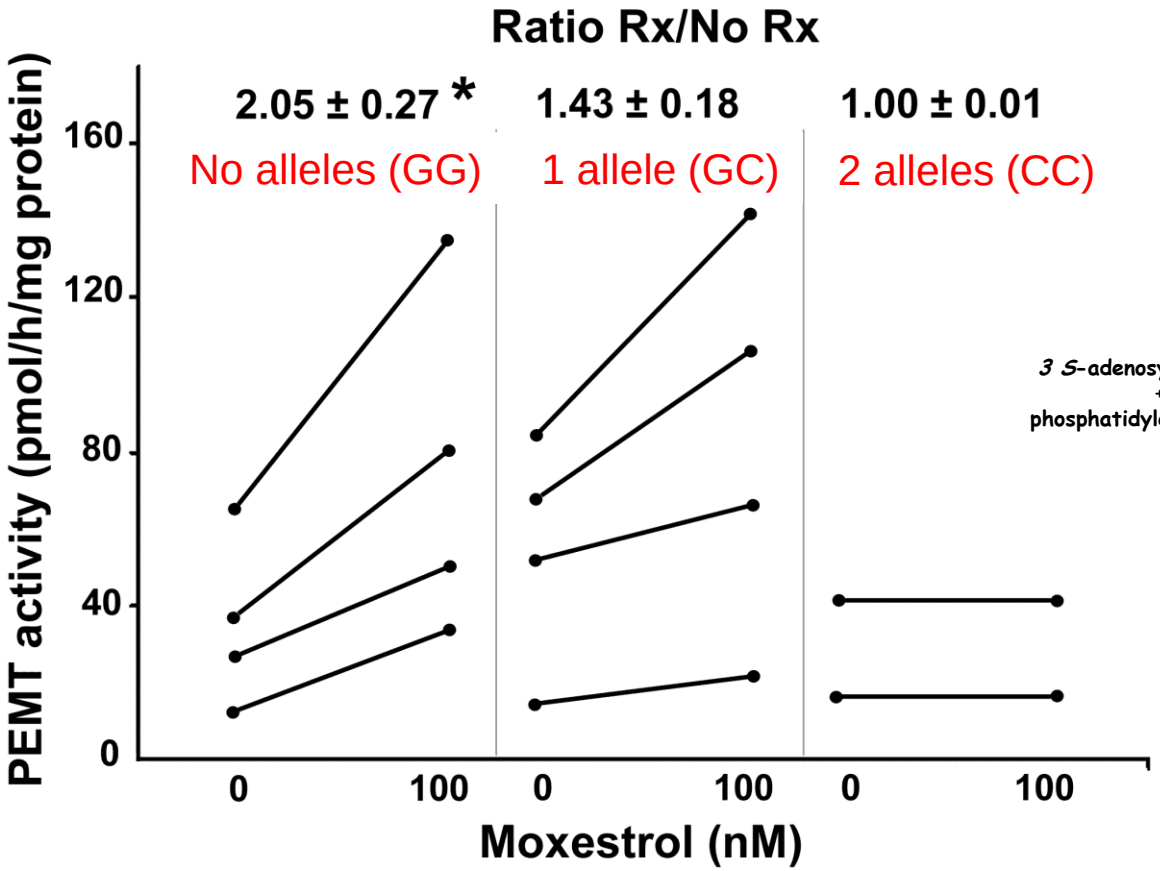
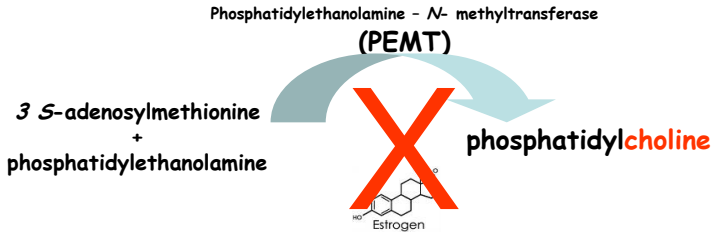
PEMT rs12325817 results in no response to estrogen





Primary human hepatocytes. Rs12325817; Rx moxesterol for 24 h.

J. Biol. Chem. 2011;286:1649-1658

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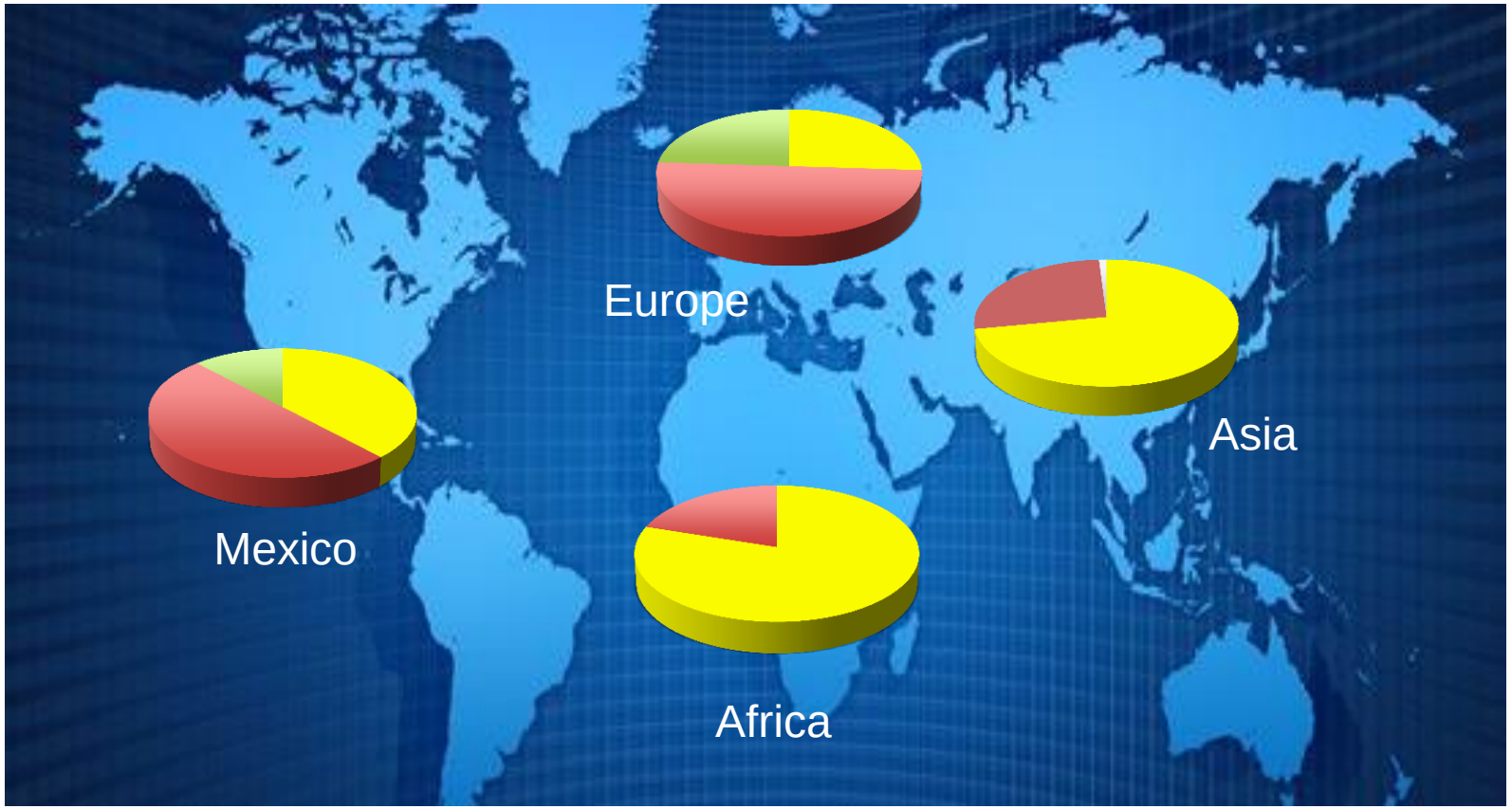
PEMT rs12325817 frequency



GG GC CC

Need more choline

rs12325817 *PEMT* G→C

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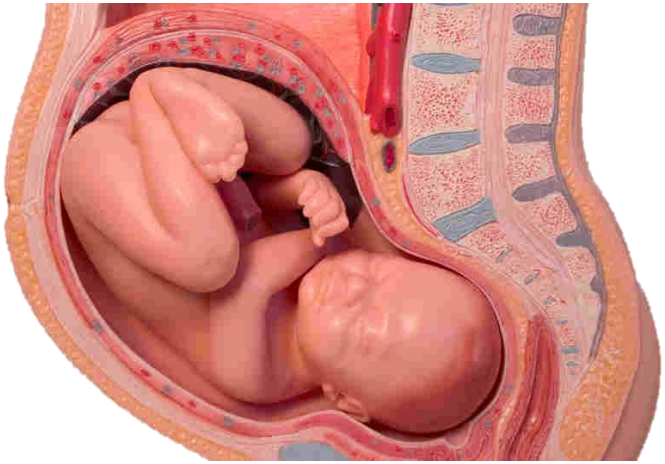
Women are special because the fetus & infant need this nutrient



….. And many women are sensitive to dietary choline intake because they have SNPs

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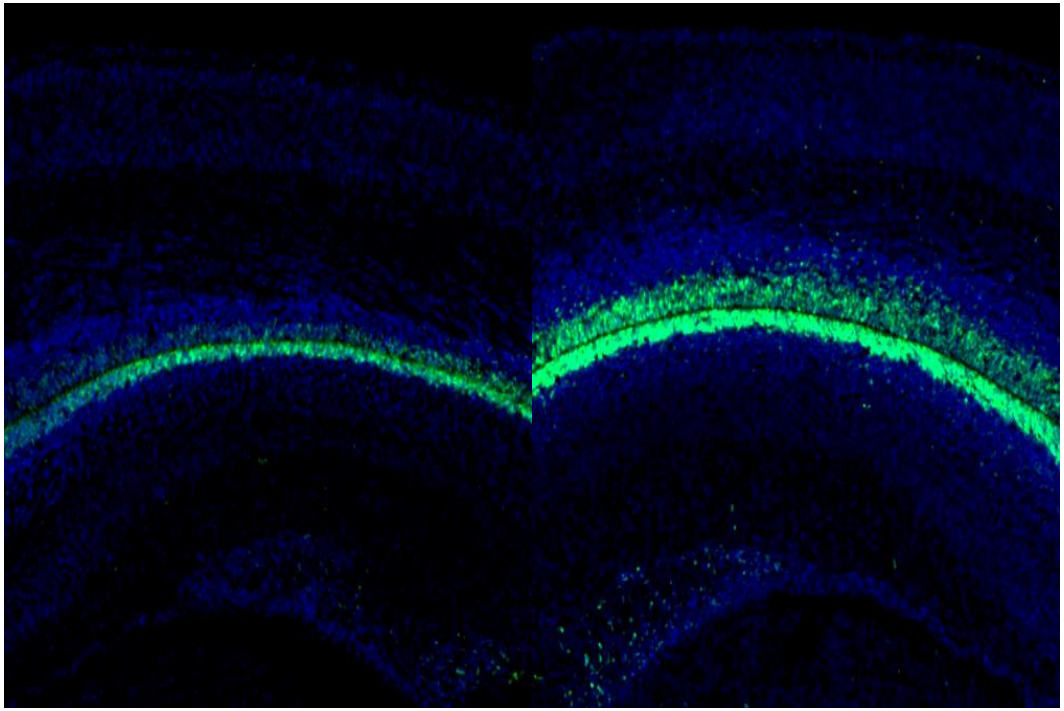
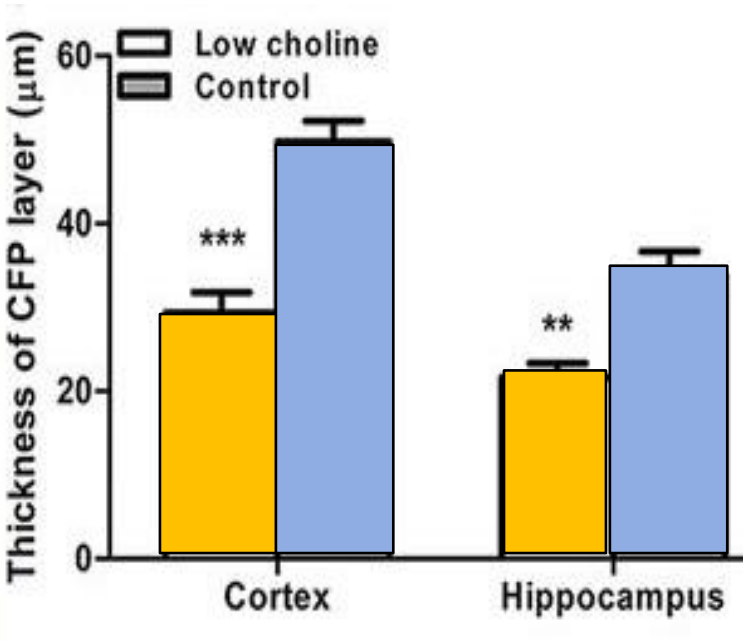
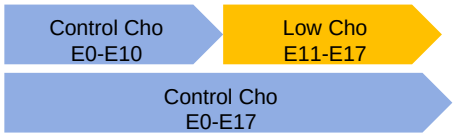
Fewer neural progenitor cells in low choline

Nestin-CFPnuc mouse E17



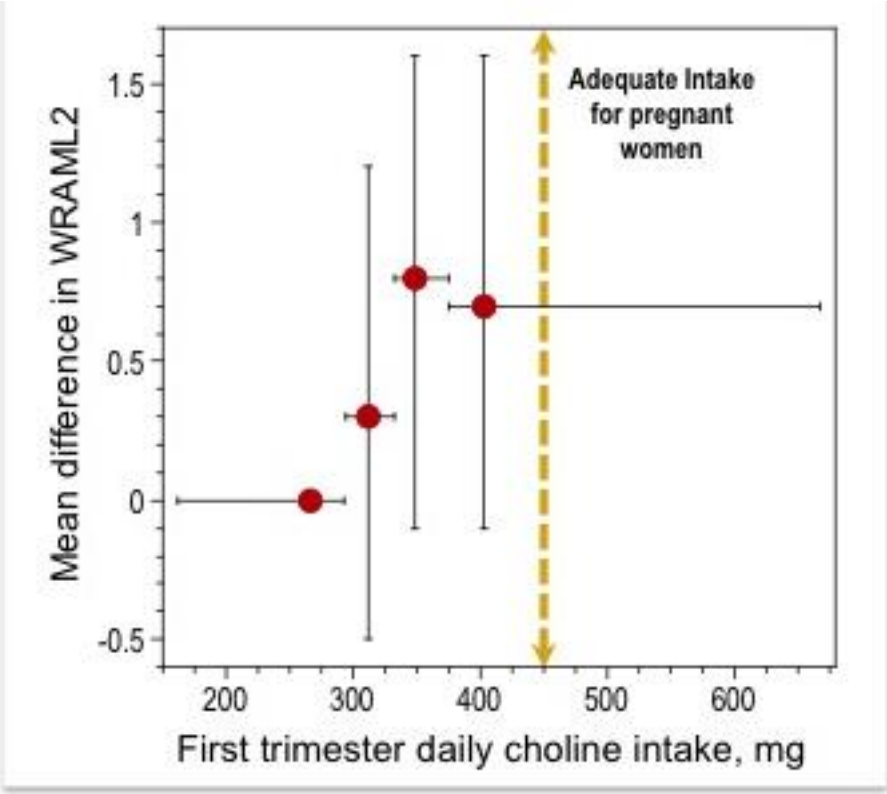
Low choline Normal choline

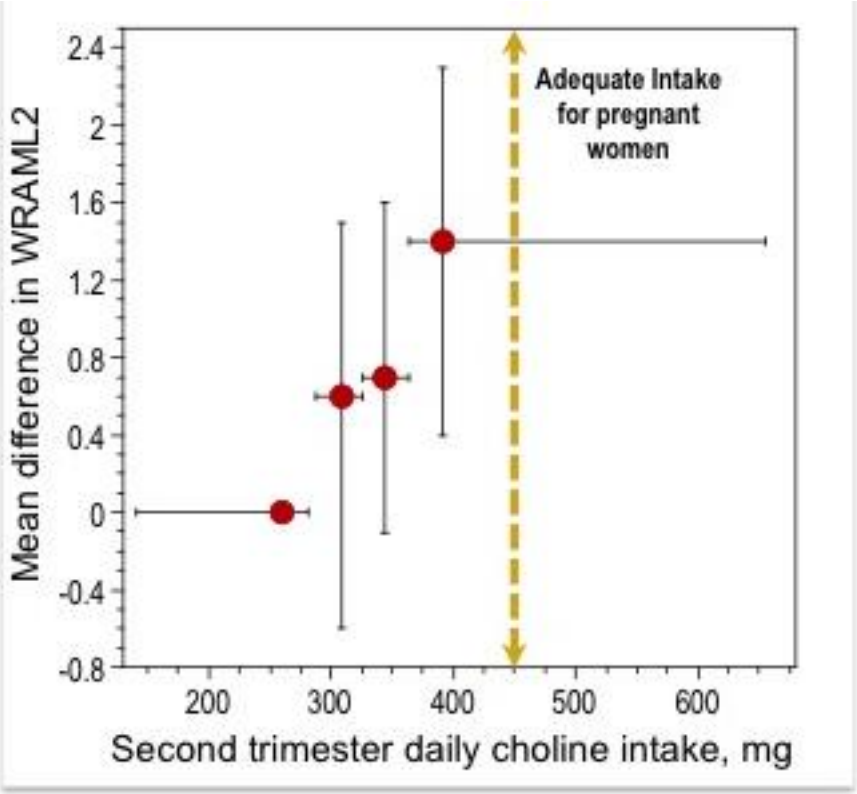




Yanyan Wang et al. FASEB J 2016;30:1566-1578

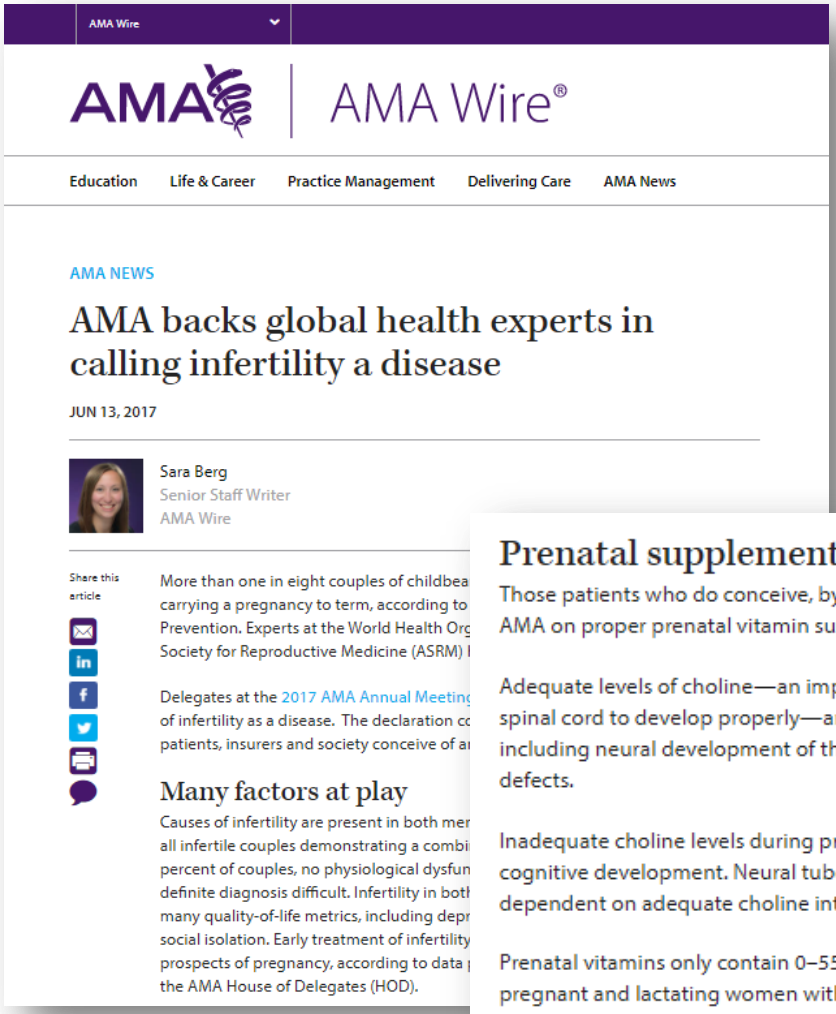
1st & 2nd Trimester maternal choline intake predicts memory in child at 7 yr

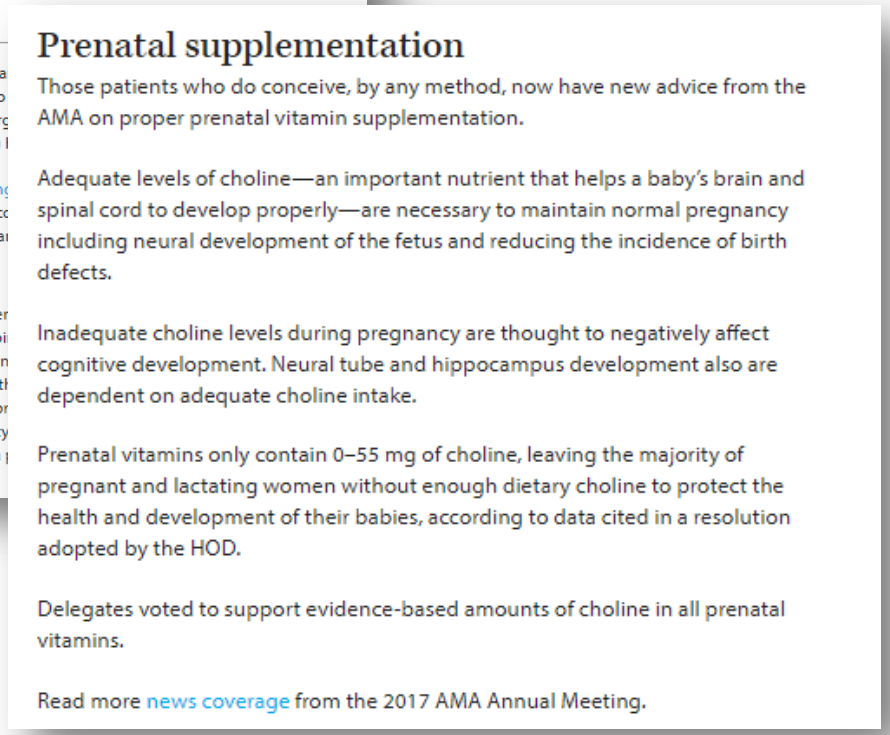




Wide Range Assessment of Memory and Learning, Second Edition (WRAML2), Design and Picture Memory subtests at age 7 y among 890 mother-child pairs in Project Viva, eastern Massachusetts, 1999–2002 to 2008–2011.

Replotted from:
Boeke C E et al. Am. J. Epidemiol. 2013;177:1338-1347





The American Medical Association (AMA) recently announced it will support actions to boost choline amounts in prenatal vitamins!

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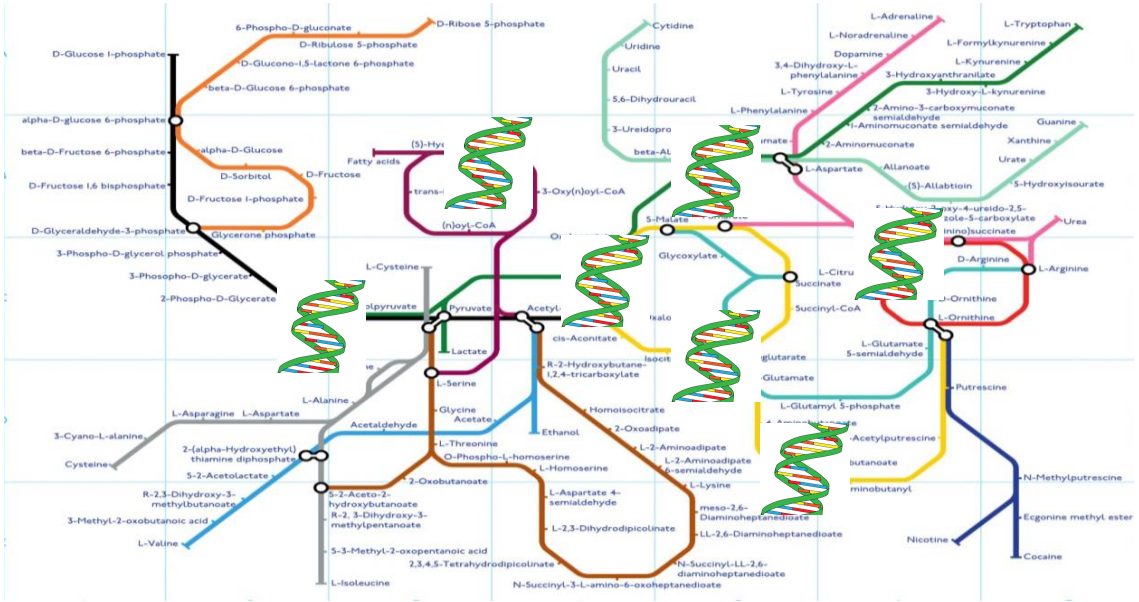
Gene-guided Intervention

Problem: Women who depend on dietary choline supply because of SNPs that make them require more choline.

Intervention: Gene test and prenatal vitamin mix containing adequate choline supply.

Moving from one SNP to complex multiple SNPs involved in metabolic pathways.



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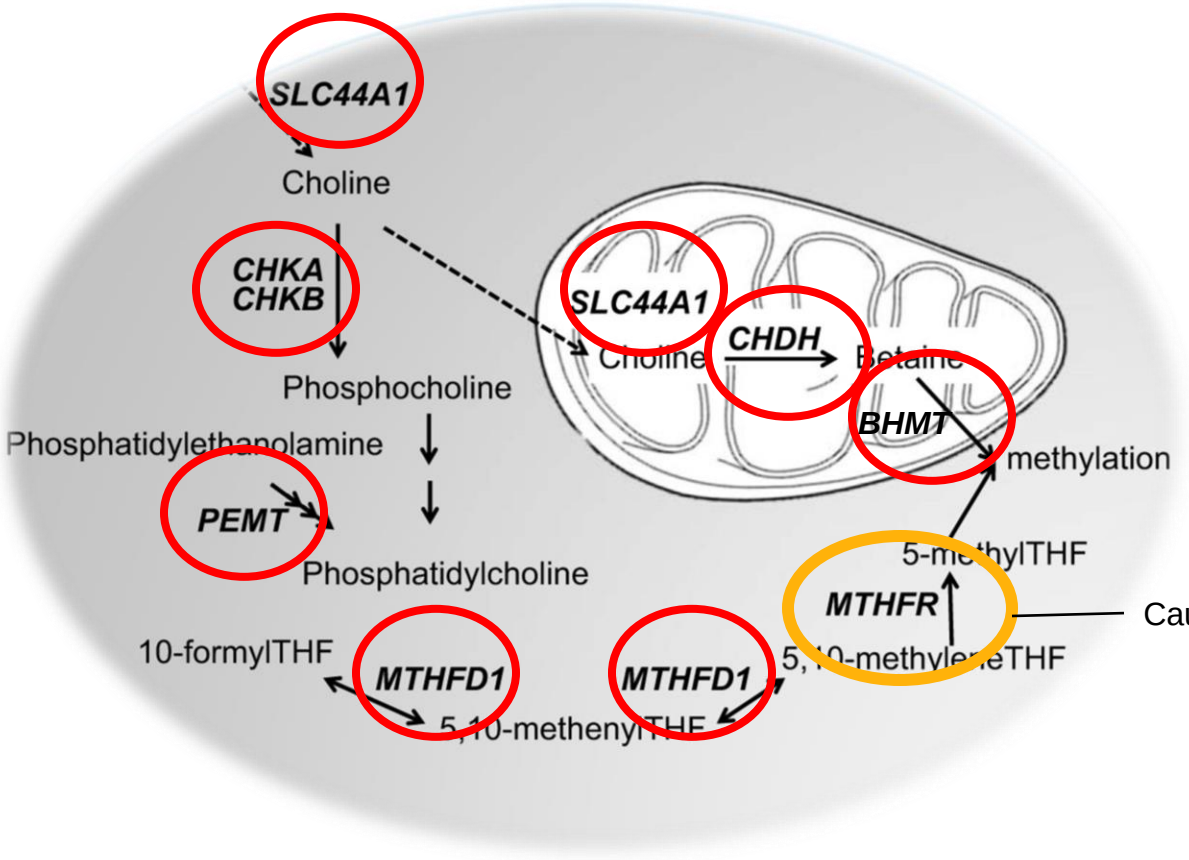
Common SNPS alter sensitivity to low choline



Caudill *et al*. J Nutr. 2009 139:727-33

*FASEB J. 2006;*20, 1336–1344; 2014;28:2970-2978
Proc.Nat.Acad.Sci. USA 2005; 102: 16025-16030

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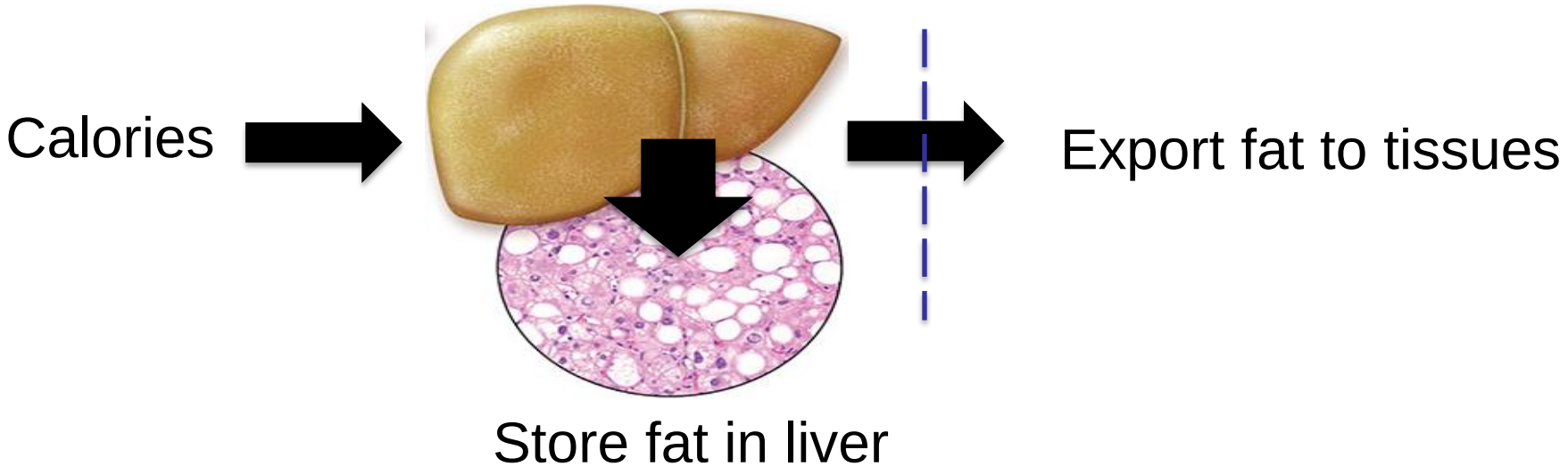
Choline deficiency presents differently – Why?

Of people who develop organ dysfunction

- **90% develop fatty liver**
- 10% develop muscle damage



Choline needed for exporting fat from liver.

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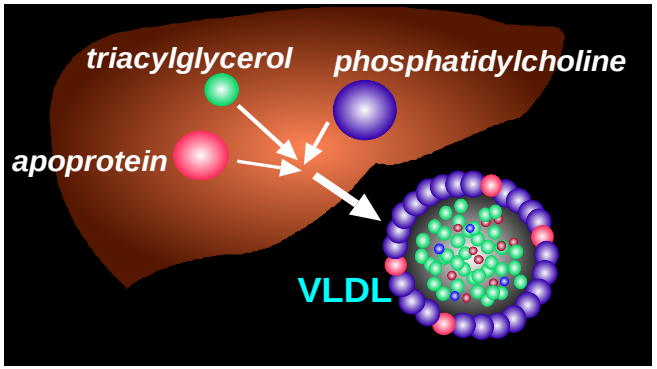
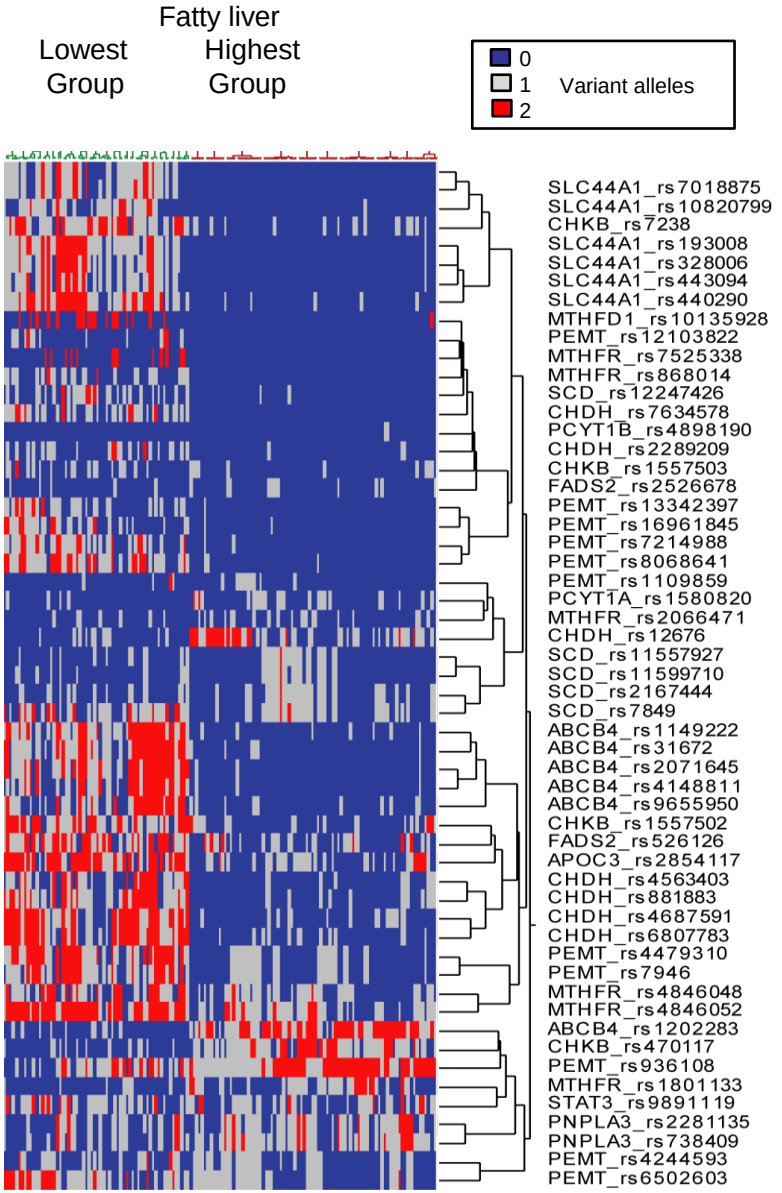
NAFLD predicted by choline SNPs





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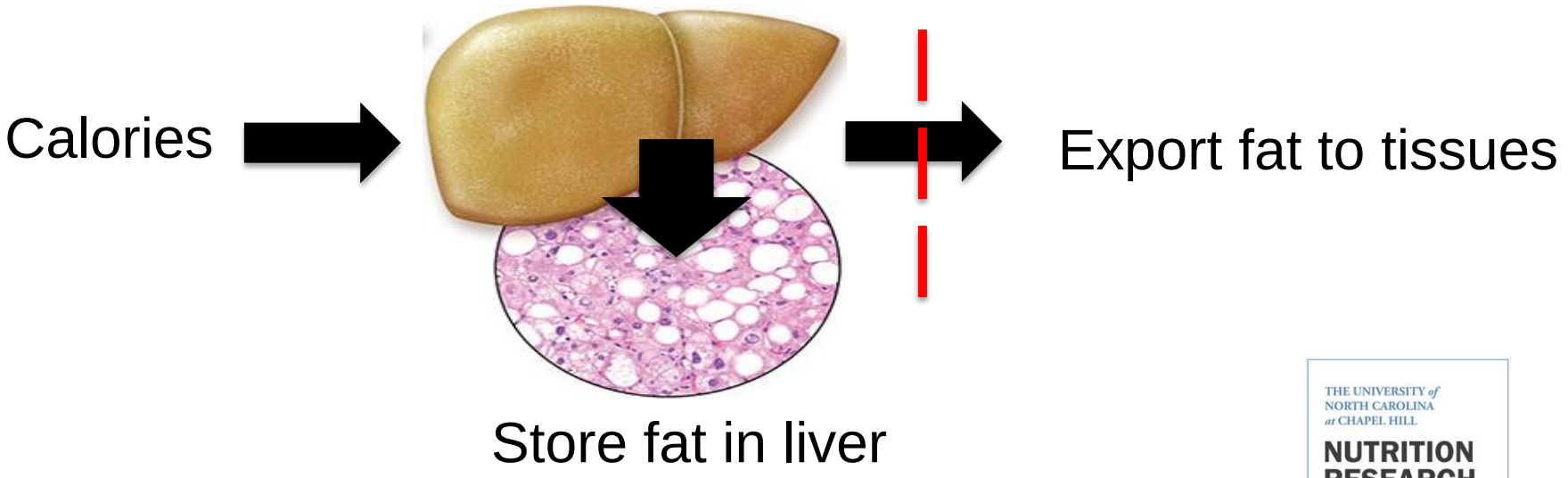
FASEB J. 2013 27:1674-89

More than just choline

SNPs in pathways of choline, folate, fatty acid transport and metabolism.

FASEB J. 2013 27:1674-89



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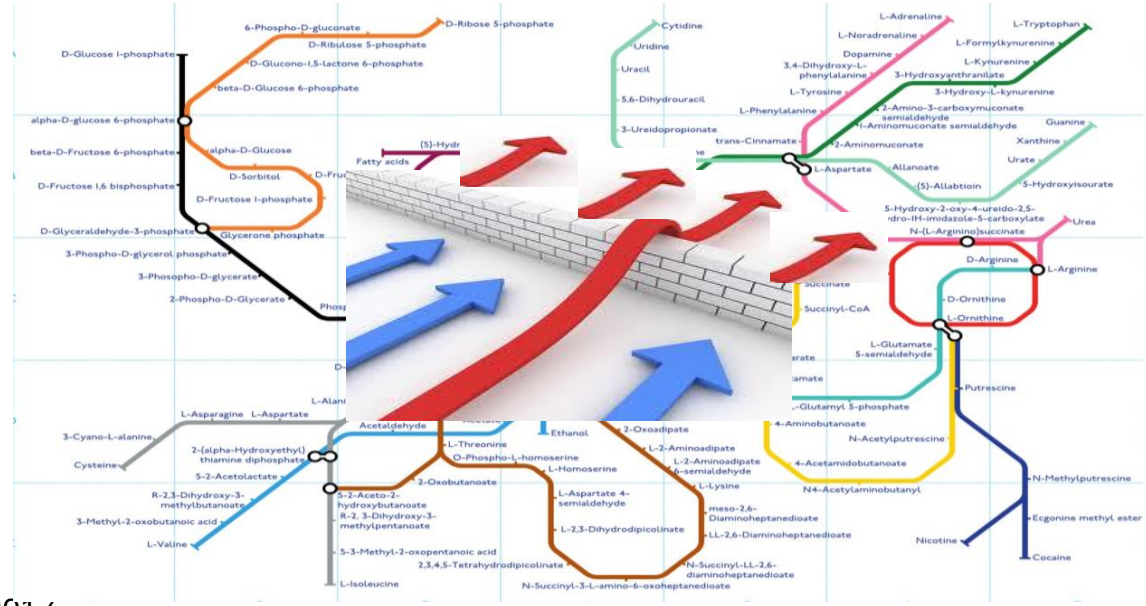
Gene-guided Intervention

Problem: People with SNPs in 21 genes are at greater risk for developing fatty liver as they gain weight.

Intervention: Medical food that delivers metabolites that bypass blocks in these specific pathways.



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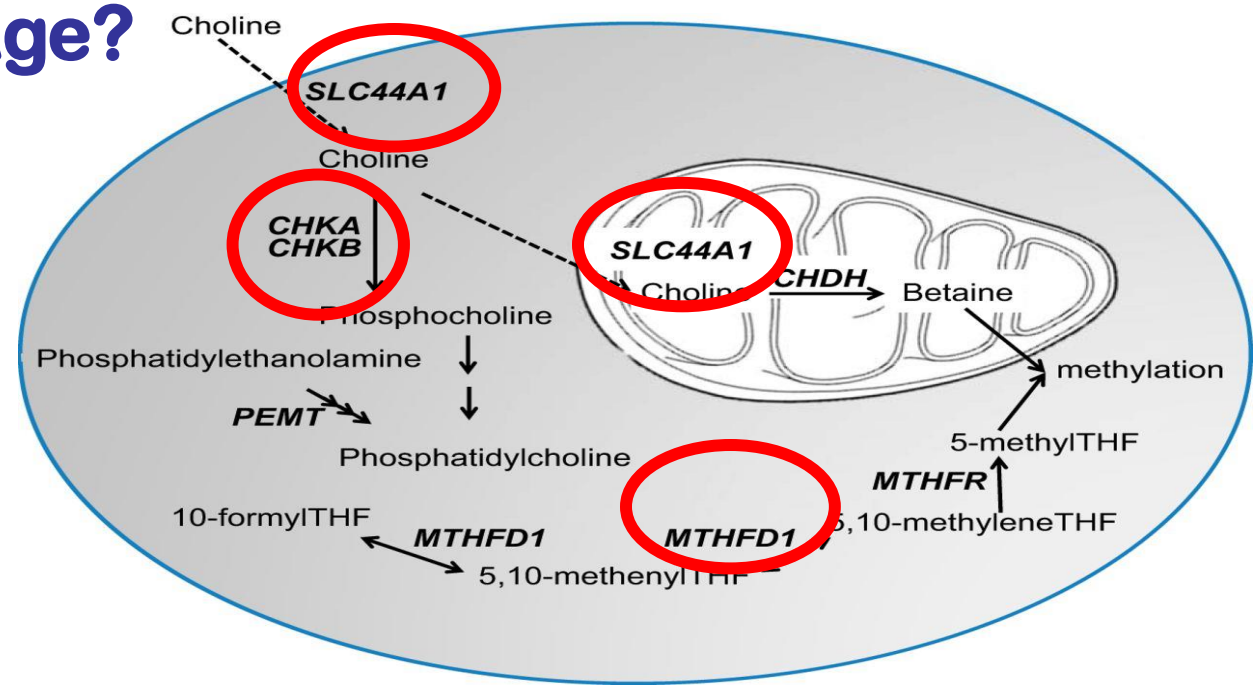
Choline deficiency presents differently – Why?

Of people who develop organ dysfunction

- **90% develop fatty liver**
- **10% develop muscle damage**

Why low choline in 10% of people results in muscle damage?



Rhabdomyolysis

SLC44A1 rs440290-rs2771040 T-G haplotype were 12x as likely to have rhabdomyolysis.

9 of 10 people affected had both *SLC44A1* rs2771040 (G) and *CHKB* rs1557502 (A) ($p<0.0001$)

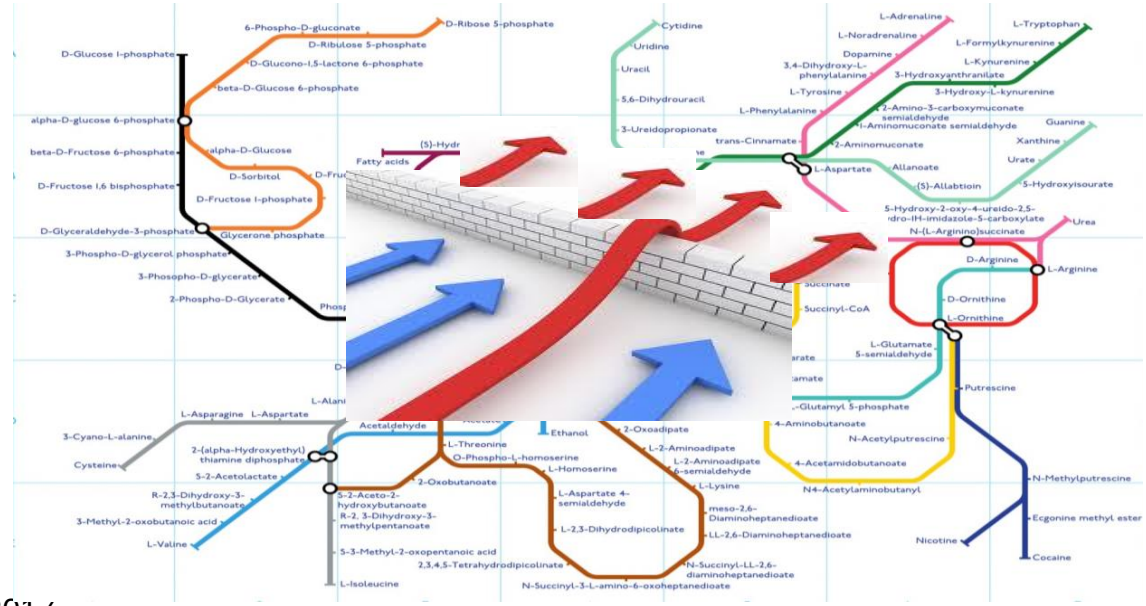
Marine officer candidates with high serum CK levels more often had the *MTHFD1* rs2236225 A allele than did men with normal CK levels (odds ratio 2.84, $p=0.05$).

FASEB J. 2014 28:2970-8.

Gene-guided Intervention

Problem: People with SNPs in multiple genes are at greater risk for developing rhabdomyolysis when they exercise

Intervention: Medical food that delivers metabolites that bypass blocks in these specific pathways.



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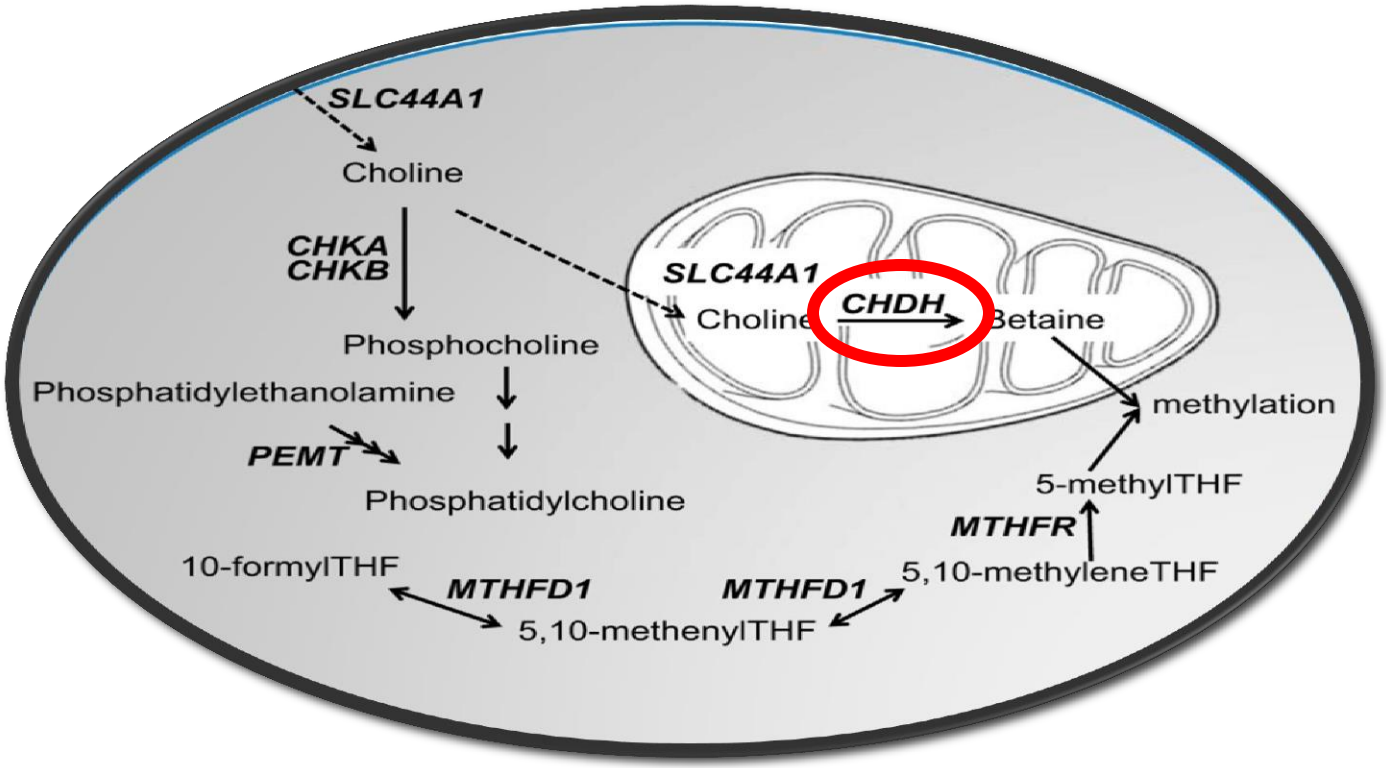
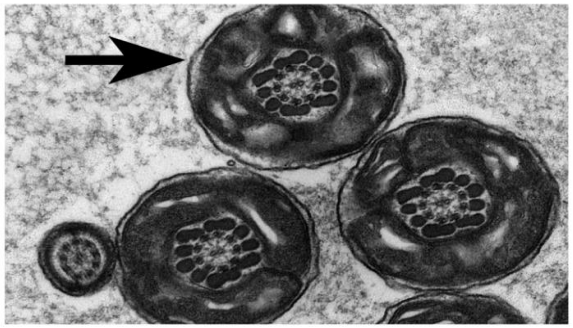
SNPS and sperm dysfunction

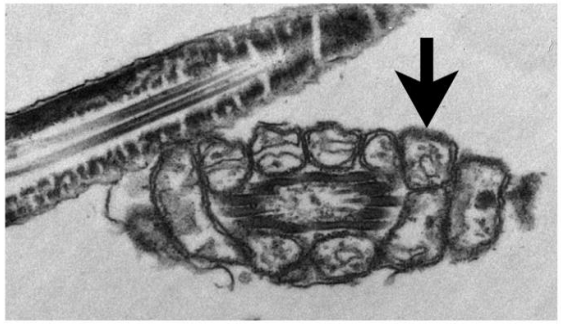


FASEB J. 2014 28:2970-8.

Deletion of *Chdh* results in dysmorphic mitochondria



+/+



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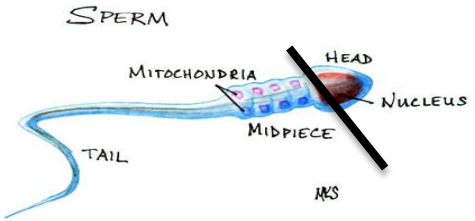

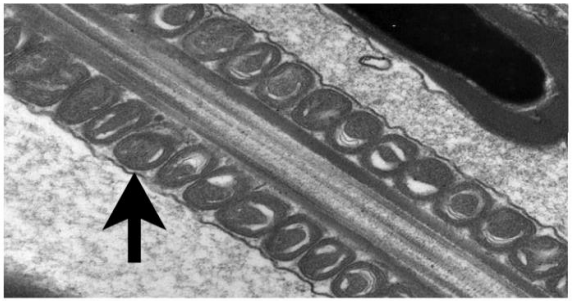

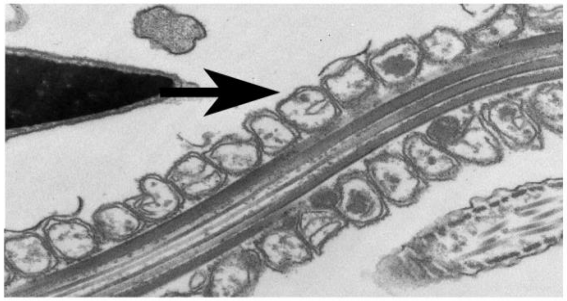

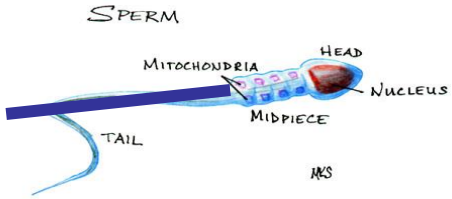

FASEB J. 2010;24:2752-2761

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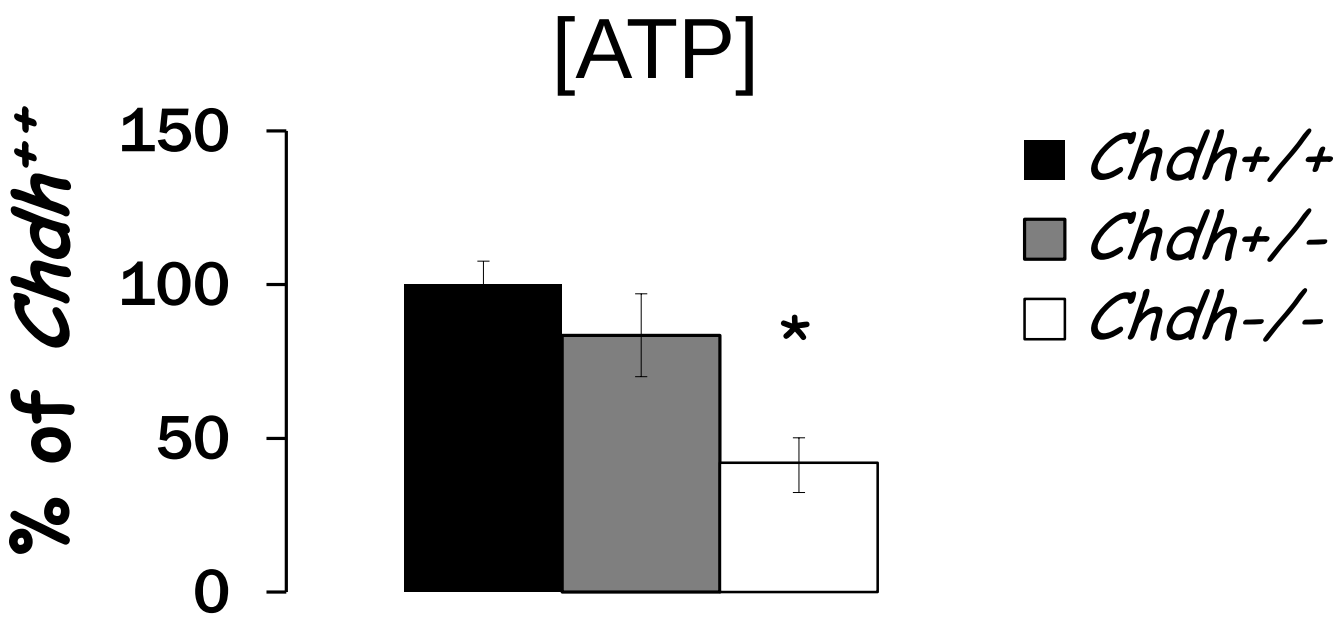
Deletion of *Chdh* results in low ATP



*FASEB J.*2010;24:2752-2761

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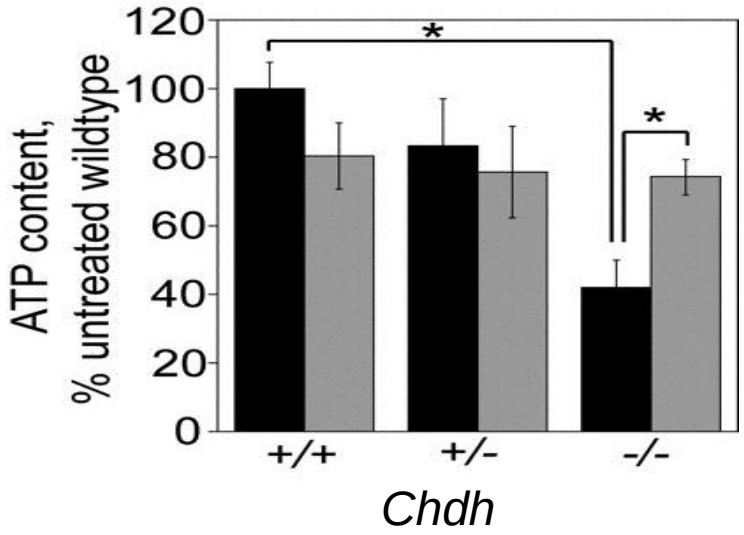
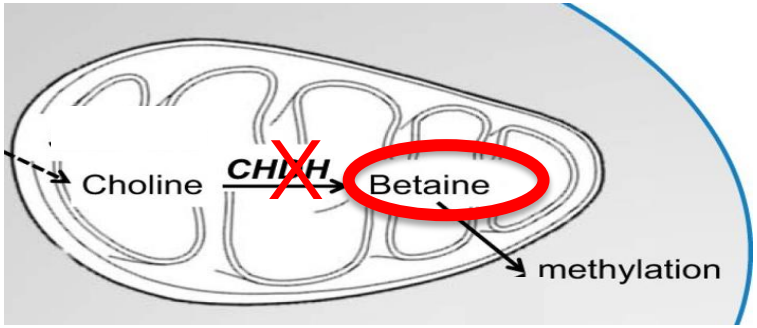
Betaine restores ATP





No betaine +betaine

*FASEB Journal 24:*2752-2761, 2010

Men with *CHDH* rs12676 G233T

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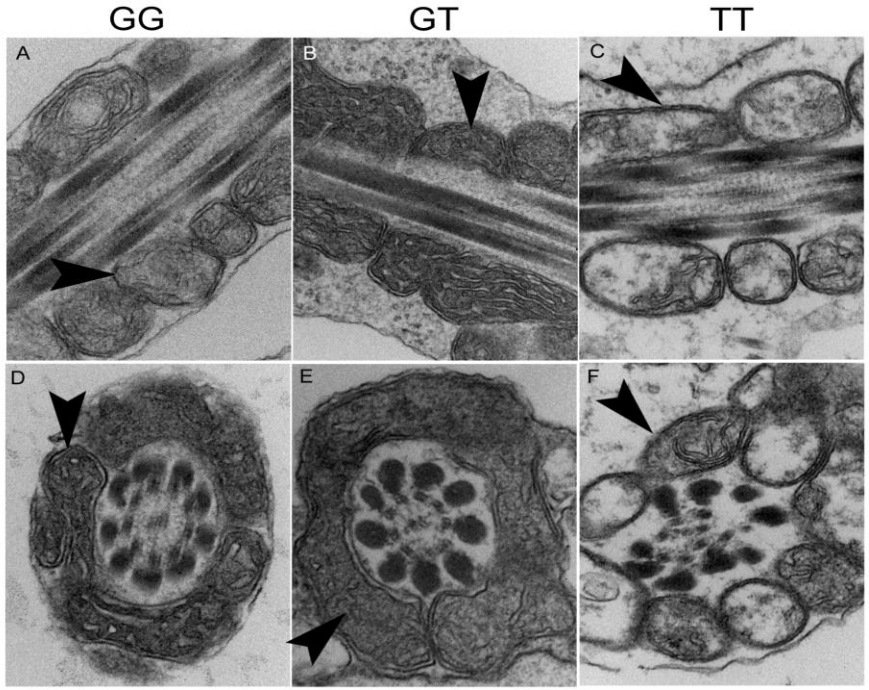
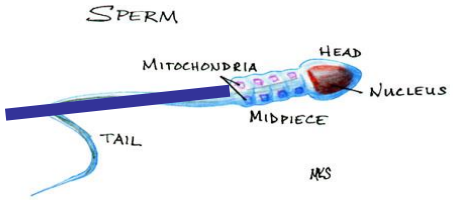
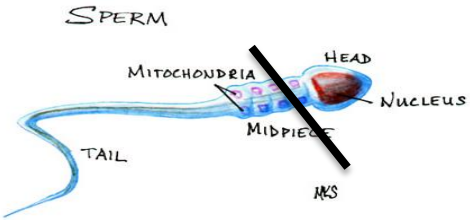
CHDH rs12676 G233T have dysmorphic mitochondria







PLoS One. 2012;7::e36047. doi: 10.1371/journal.pone.0036047

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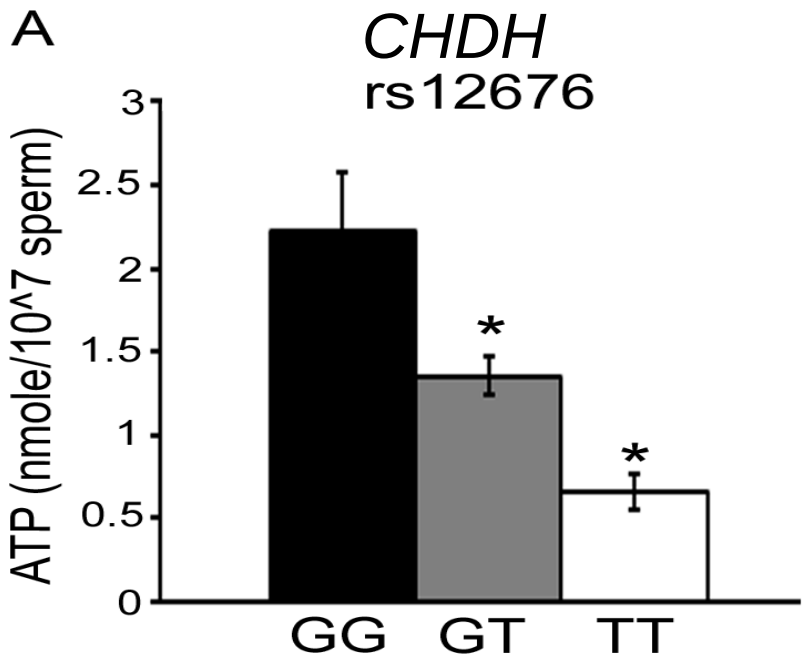
CHDH rs12676 G233T have low ATP



PLoS One. 2012;7:e36047. doi: 10.1371/journal.pone.0036047

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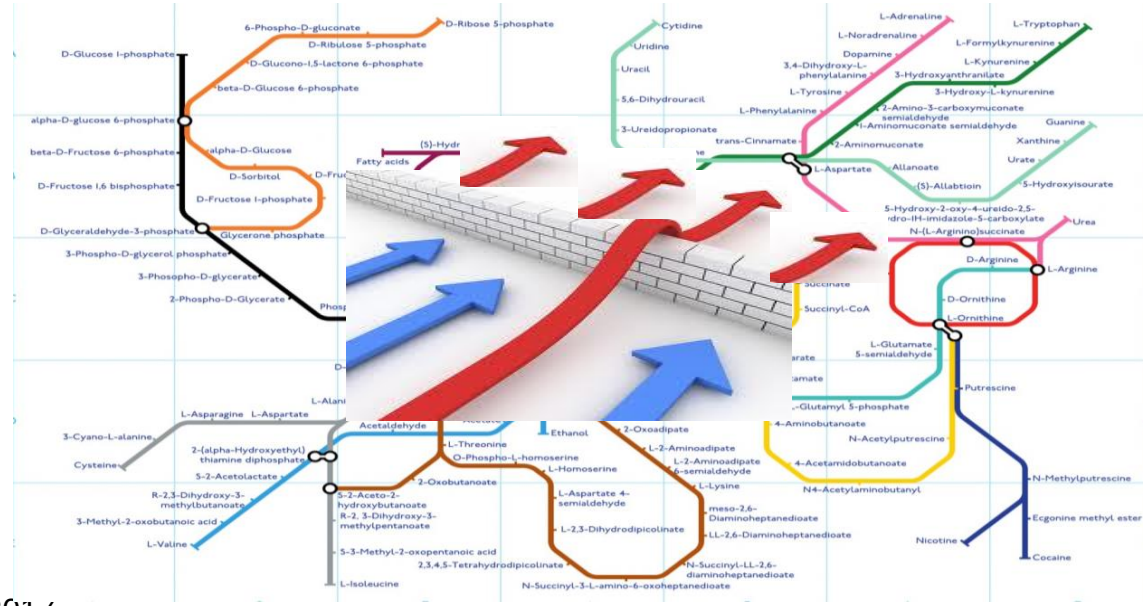
Gene-guided Intervention

Problem: Men with SNPs 1-carbon genes are at greater risk for developing low sperm ATP.

Intervention: Delivers metabolites that bypass blocks in these specific pathways.



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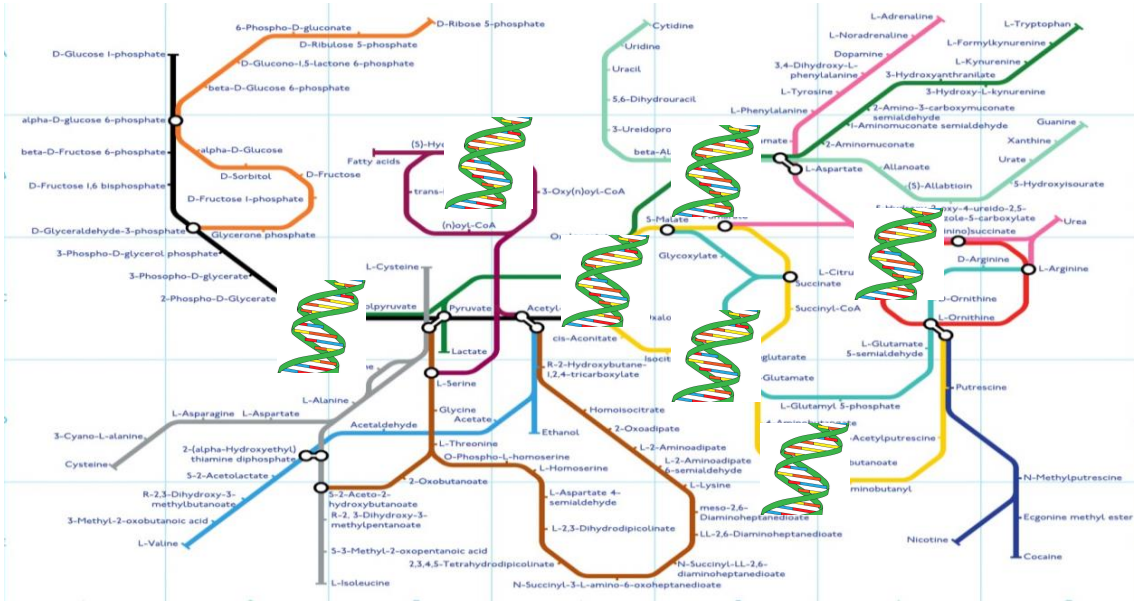
Future developments:

Better methods for moving from one SNP analyses to complex multiple SNPs involved metabolic pathways.



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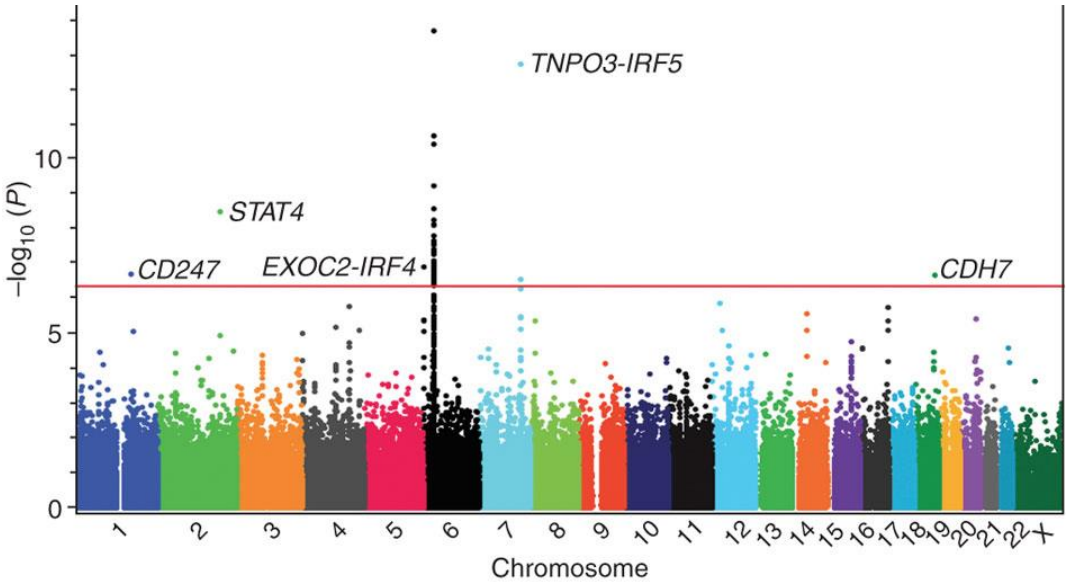
Including Diet intake (diet challenges) in GWAS studies



Need to look at people challenged by low or high intake.

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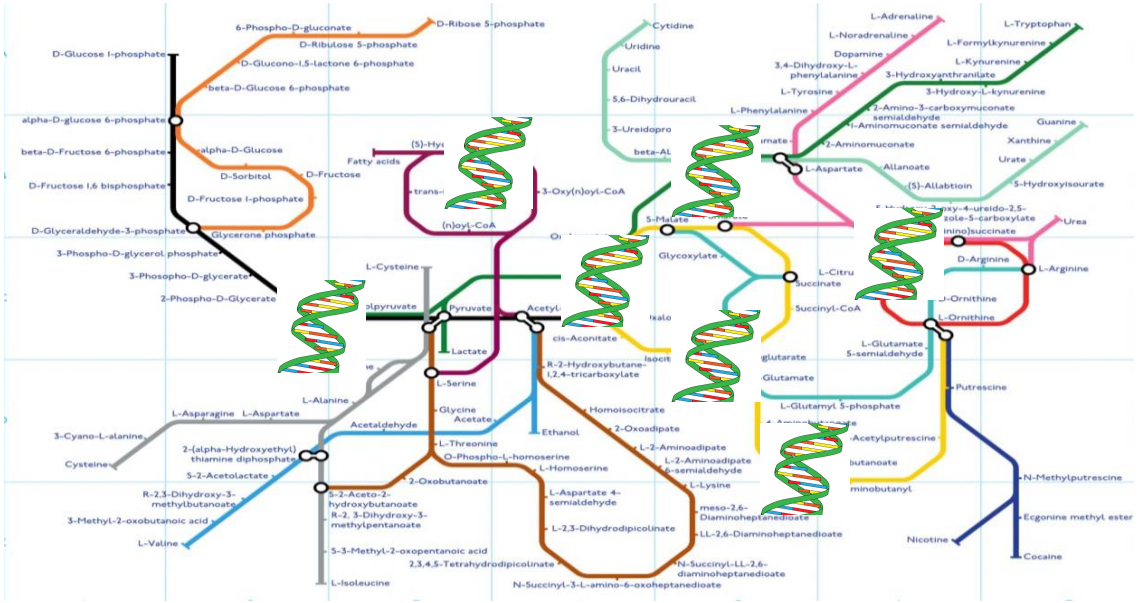
Use of genetic information to identify people with genetically-caused inefficiencies in metabolism that cause health problems



Deliver metabolites that bypass these metabolic problems to manage health problem.

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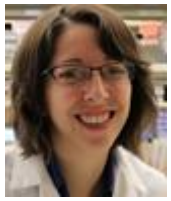
Thank you


N. Surzenko


Y. Wang


I. Trujillo


E. Pjetri


J. Owen


S. Orena


C. Munson

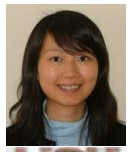

W. Friday


A. Johnson


K-A. da Costa


M. Spencer

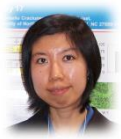

S. Goodson


W. Sha


Y-W. Teng


L. Fischer


E. Yen


X. Zhu


D. Reed


M. Niculescu


K. Corbin


C. Craciunescu

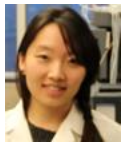

J. Song


T. Benton


M. Mehedint


M. Resseguie


H-M. Hwang


X. Zhou


D. Lupu

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