Gene-guided NutritionInterventions

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Steven Zeisel Disclosures

AFFILIATION/FINANCIAL CORPORATE ORGANIZATION

INTERESTS

Grants/Research

Support:

NIH, USDA, Balchem

Scientific Advisory

Board/Consultant:

Metabolon, CFEN, SNPitty,

Enzymotec, Ingenuity Foods,

Second Science

Speakers'

Support/Honorarium:

Balchem, Nutrapharma

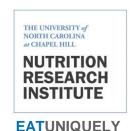
Stock Shareholder: Zthera

Other Financial or

Material

Support/Honorarium:

None

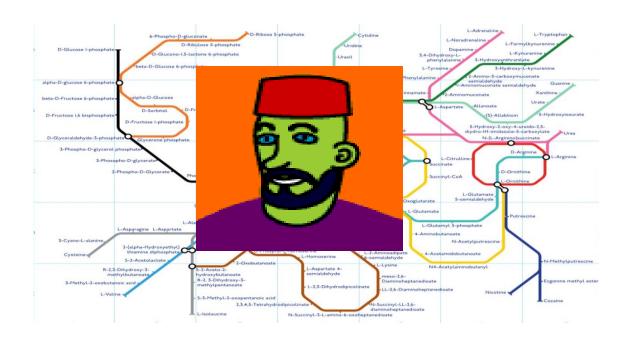




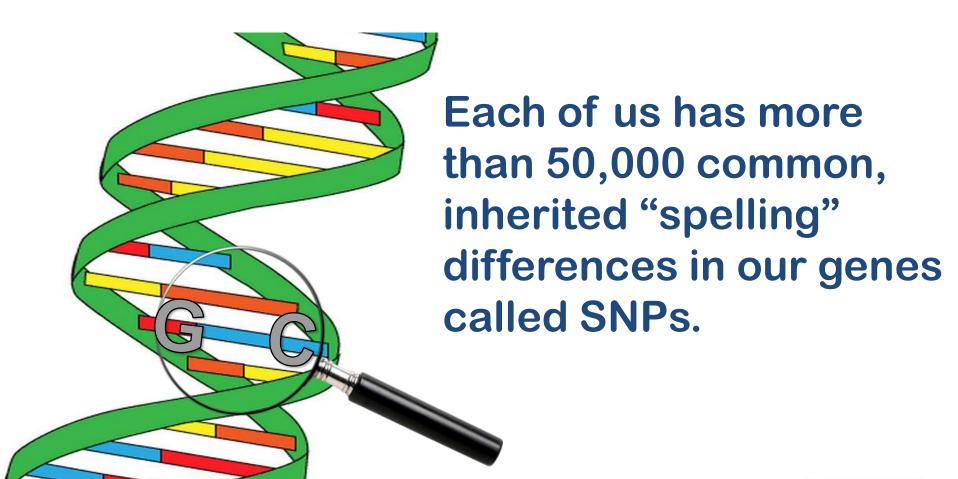
Gene-guided medical foods www.zthera.com



Modern science tells us that people are metabolically different

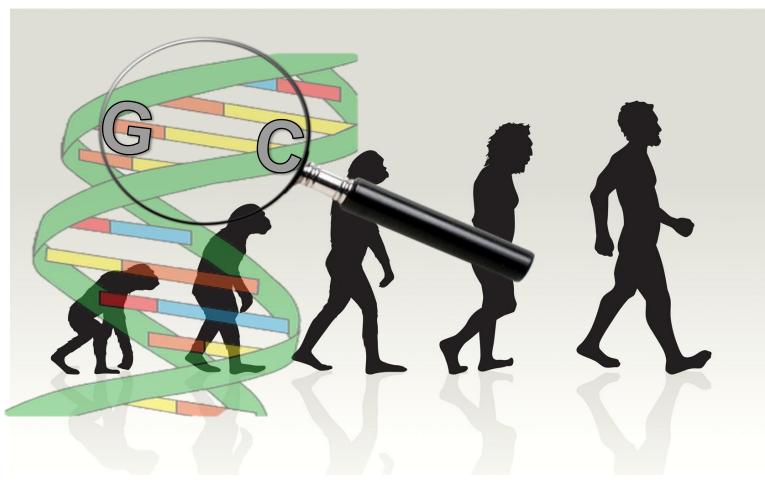






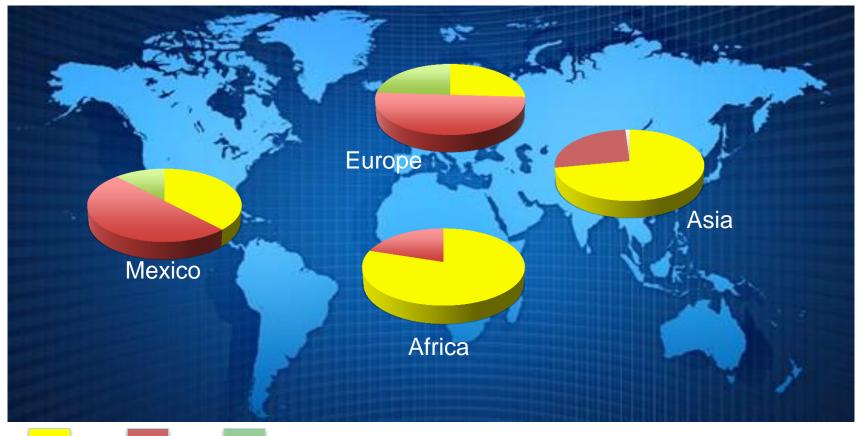


We inherited them from our ancestors.





Populations differ in distribution of many SNPS





Need more choline

rs12325817

PEMT G→C



Populations differ in distribution of many SNPS



Populations differ in distribution of many SNPS

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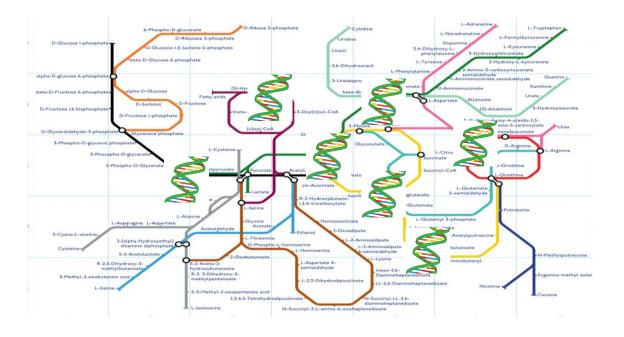
Normal nutrition is composed of many metabolic pathways that nutrients must transit.







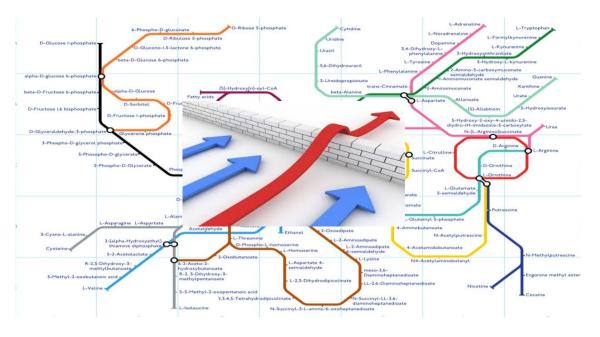
Each of these pathways depends on many genes.





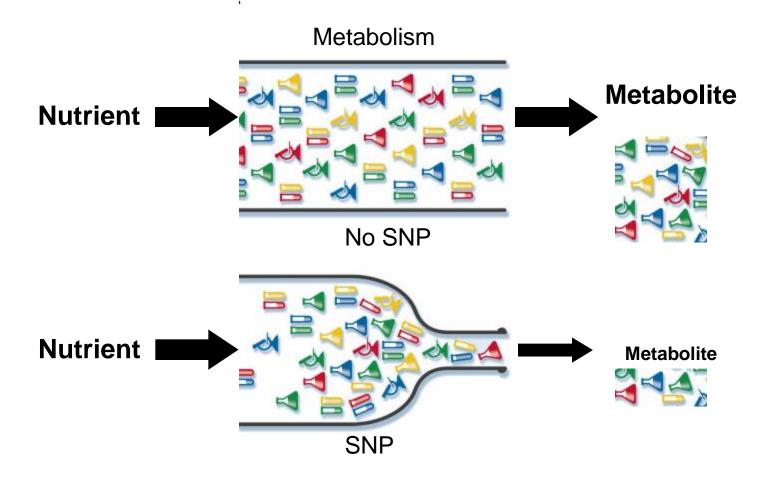


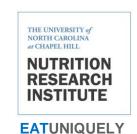
When these genes are polymorphic (alternatively "spelled"; SNPs), roadblocks in metabolism can occur



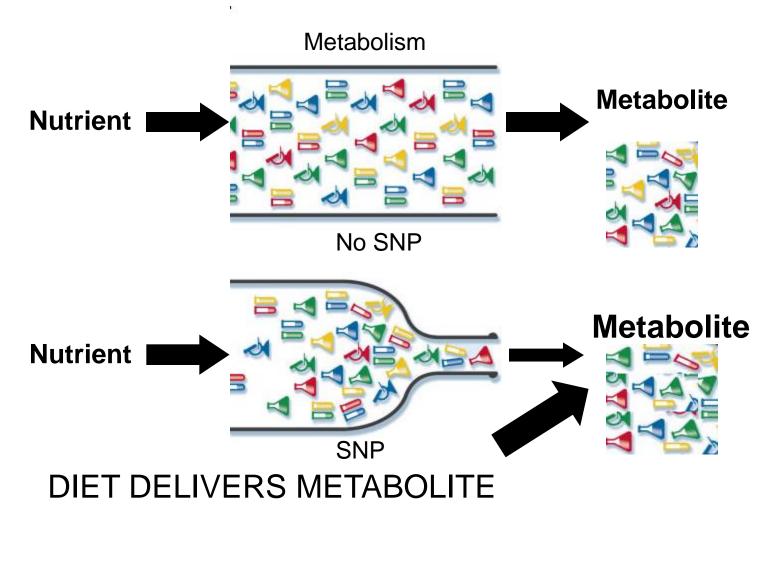


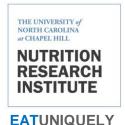
These genetic roadblocks can make metabolism inefficient



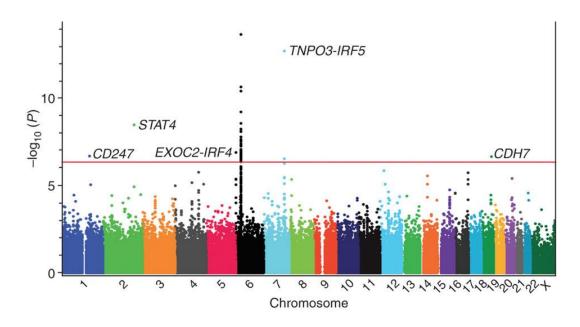


Diet may bypass roadblock caused by SNP



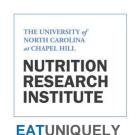


Diet intake is often missing in GWAS studies



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

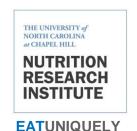
Need to look at people challenged by low or high intake.



Our work on expanding the catalog of metabolically important SNPs

CHOLINE

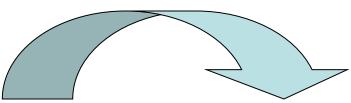
- IOM AI diet recommendation 1998
- FDA DRI 2016, good source labeling
- AMA 2016 recommends inclusion in prenatals
- Important for liver and muscle
- Critical for fetal development
- Human requirements vary by genotype



Endogenous synthesis of choline

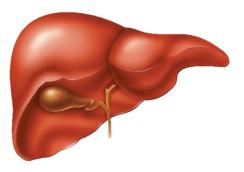
Phosphatidylethanolamine – *N*- methyltransferase

(PEMT)

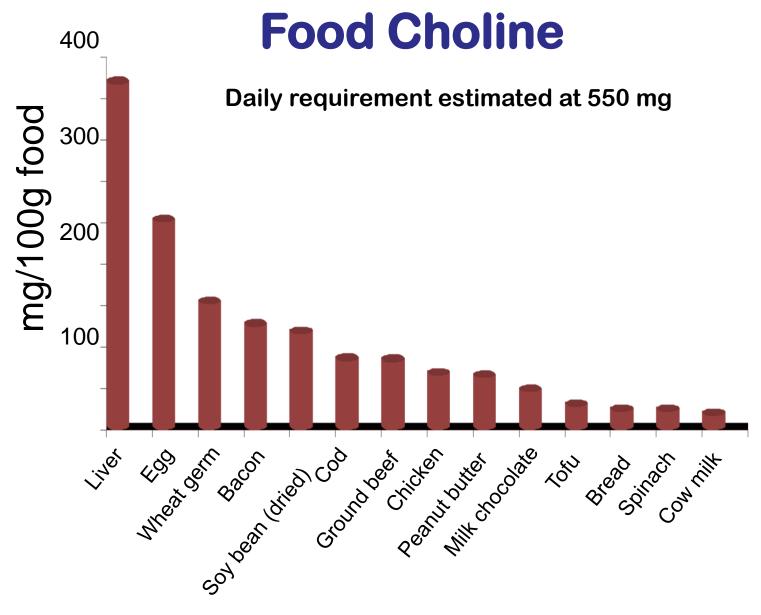


3 S-adenosylmethionine + phosphatidylethanolamine

phosphatidylcholine



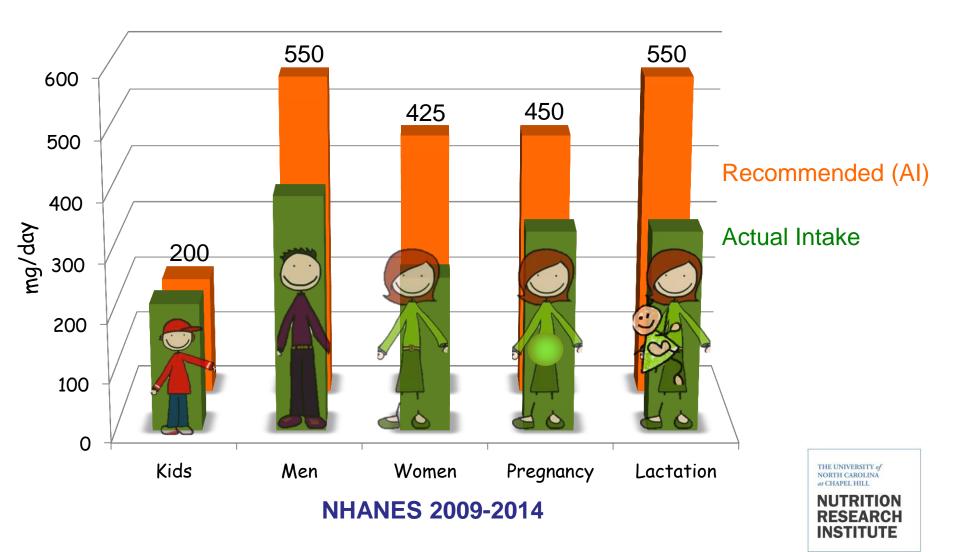






From http://www.ars.usda.gov/Services/docs.htm?docid=6232

Most Americans do <u>not</u> achieve Adequate Intake for choline.



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US Recommendations for choline

Population		Tolerable Upper
and Age	Adequate Intake	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

DIETARY REFERENCE INTAKES

ros

Thiamin, Riboflavin,
Niacin, Vitamin B₆,
Folate, Vitamin B₁₂,
Pantothenic Acid,

A Report of the
Standing Committee on the Scientific Evaluation
of Dietary Reference Intakes and its
Panel on Folate, Other B Vitamins, and Choline and
Subcommittee on Upper Reference Levels of Nutrients
Food and Nutrition Board
Institute of Medicine

Biotin, and Choline

NATIONAL ACADEMY PRESS Washington, D.C.

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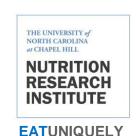
Most humans required dietary choline

Dietary requirement differs by gender

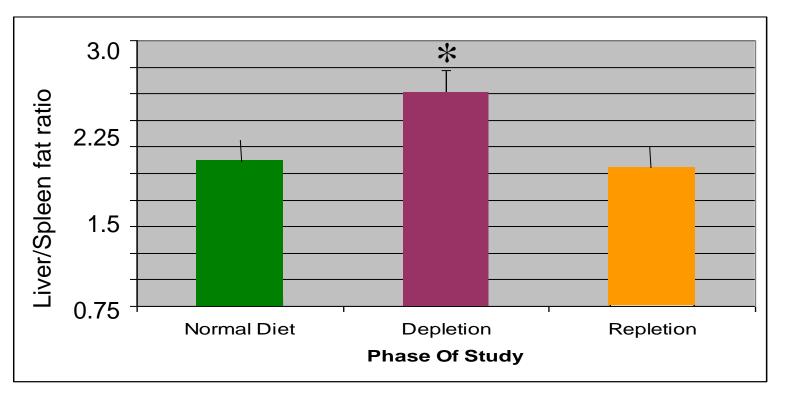


77% 80% 44%

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



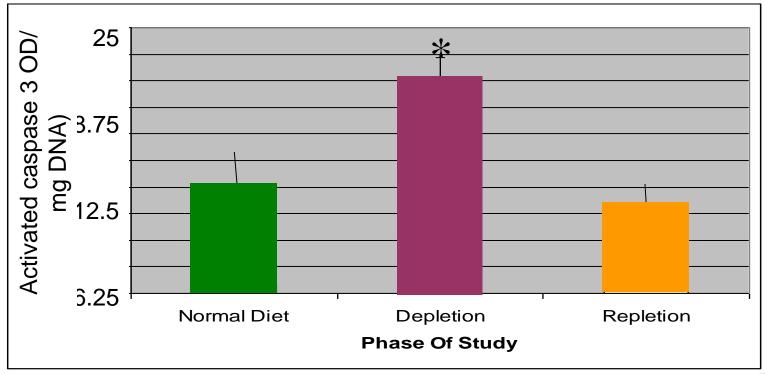
Liver fat increases





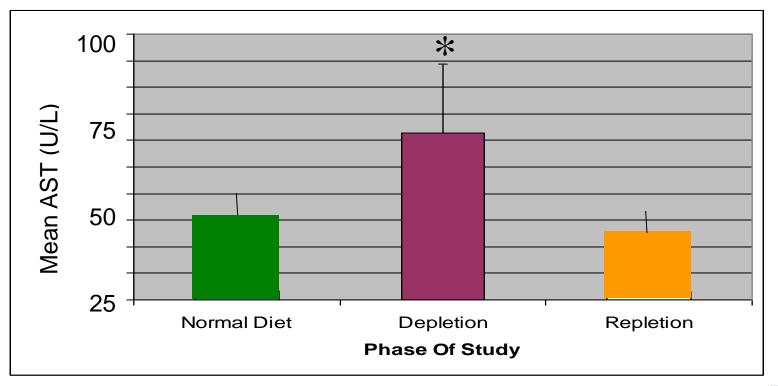


Cell suicide (apoptosis) activated in lymphocytes





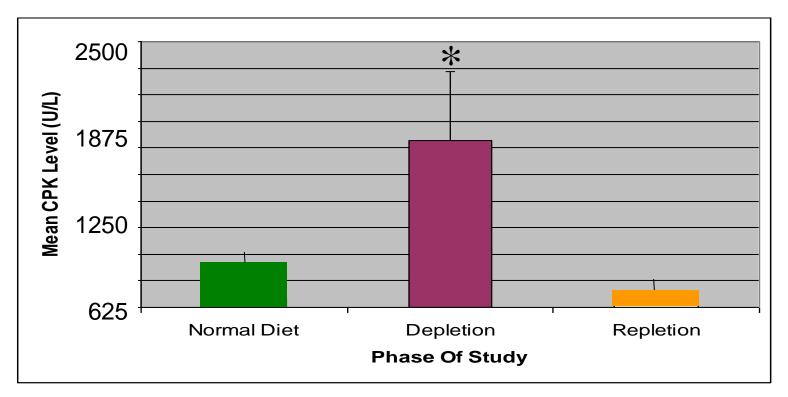
Liver cells damaged







Muscle cells damaged



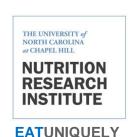




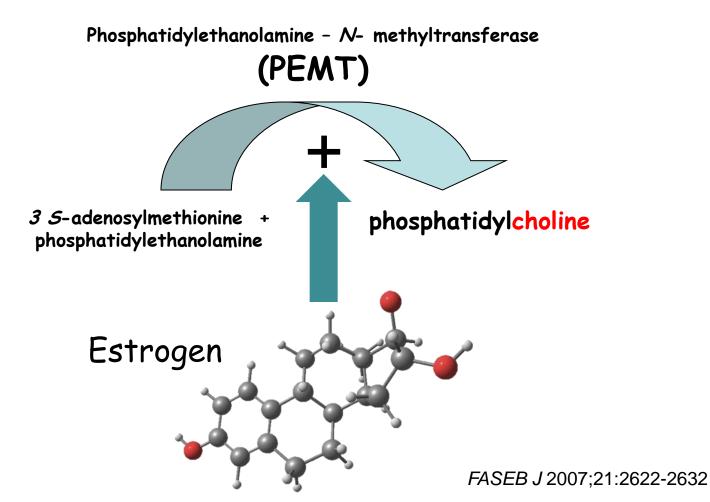
Why do some premenopausal women require less dietary choline?



Did not need to eat choline for 42 days.

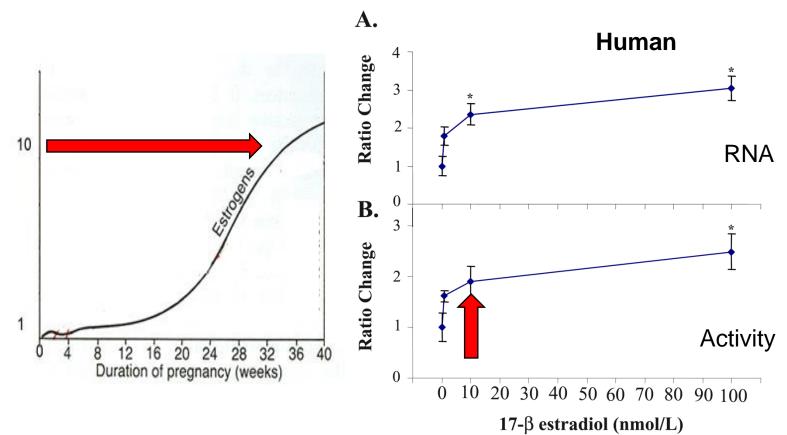


Endogenous synthesis of choline induced by estrogen





PEMT induced by estrogen



FASEB J 2007;21:2622-2632



Why do some premenopausal women still need dietary choline?



44%

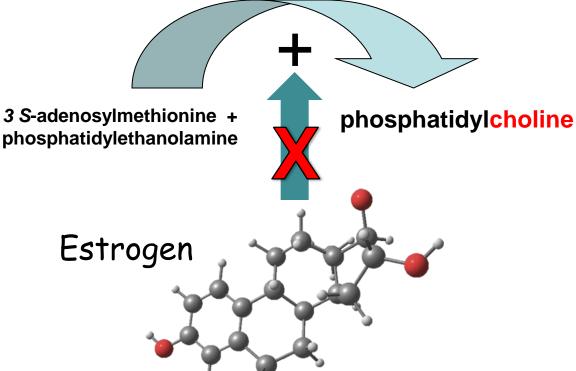
need to eat choline or they develop fatty liver and liver damage.



PEMTSNP rs12325817 prevents induction by estrogen

Phosphatidylethanolamine – *N*- methyltransferase

(PEMT)



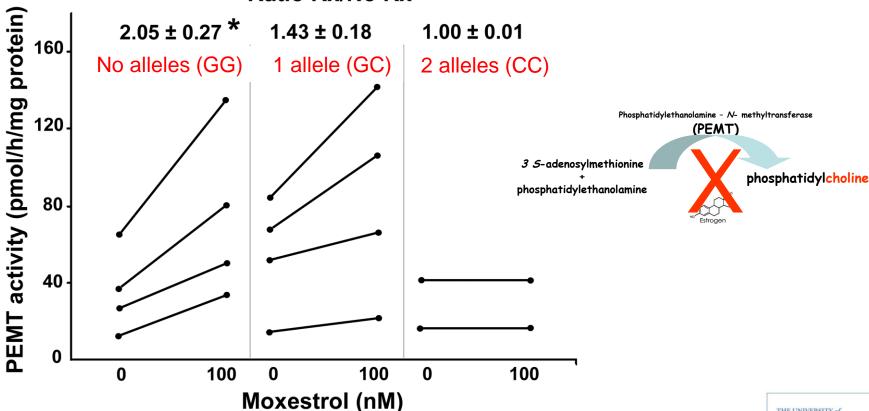
THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL.

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

PEMT rs12325817 results in no response to estrogen



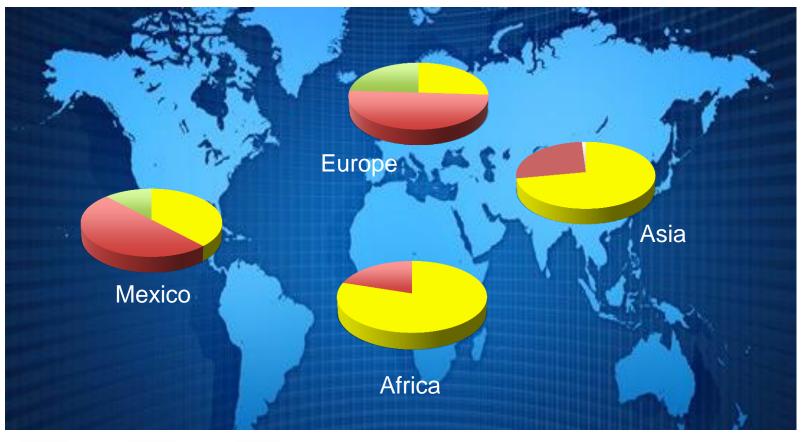


Primary human hepatocytes. Rs12325817; Rx moxesterol for 24 h.

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



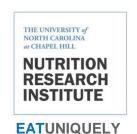
PEMT rs12325817 frequency



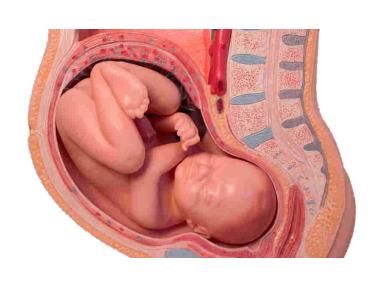


Need more choline

rs12325817 *PEMT* G→C

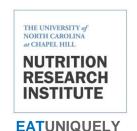


Women are special because the fetus & infant need this nutrient



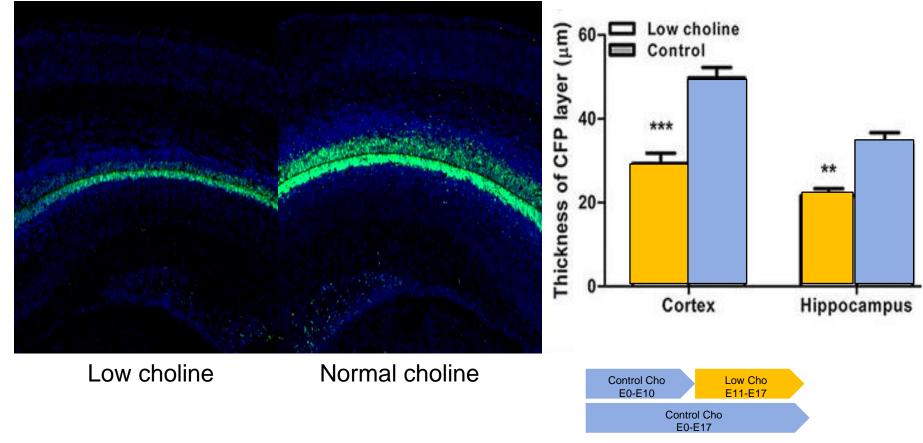


..... And many women are sensitive to dietary choline intake because they have SNPs



Fewer neural progenitor cells in low choline

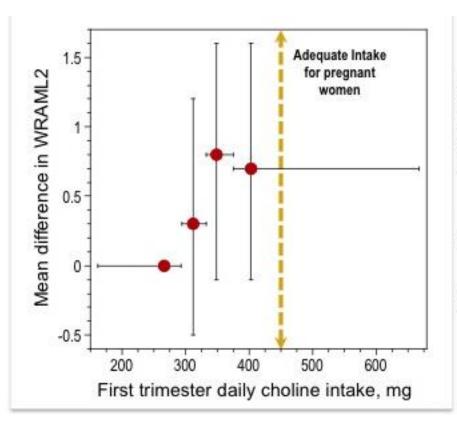
Nestin-CFPnuc mouse E17

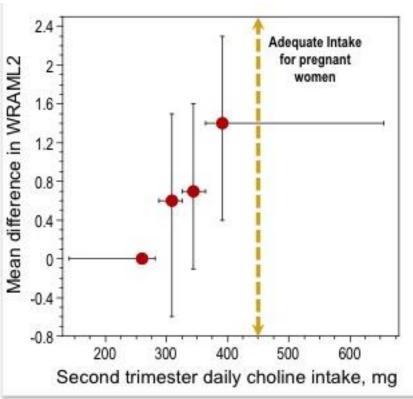






1st & 2nd Trimester maternal choline intake predicts memory in child at 7 yr





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!







More than one in eight couples of childbea carrying a pregnancy to term, according to Prevention, Experts at the World Health Orc Society for Reproductive Medicine (ASRM) I

Delegates at the 2017 AMA Annual Meeting of infertility as a disease. The declaration co patients, insurers and society conceive of ar

Many factors at play

Causes of infertility are present in both mer all infertile couples demonstrating a combi percent of couples, no physiological dysfun definite diagnosis difficult. Infertility in both many quality-of-life metrics, including depr social isolation. Early treatment of infertility prospects of pregnancy, according to data (the AMA House of Delegates (HOD).

Prenatal supplementation

Those patients who do conceive, by any method, now have new advice from the AMA on proper prenatal vitamin supplementation.

Adequate levels of choline—an important nutrient that helps a baby's brain and spinal cord to develop properly—are necessary to maintain normal pregnancy including neural development of the fetus and reducing the incidence of birth defects.

Inadequate choline levels during pregnancy are thought to negatively affect cognitive development. Neural tube and hippocampus development also are dependent on adequate choline intake.

Prenatal vitamins only contain 0-55 mg of choline, leaving the majority of pregnant and lactating women without enough dietary choline to protect the health and development of their babies, according to data cited in a resolution adopted by the HOD.

Delegates voted to support evidence-based amounts of choline in all prenatal vitamins.

Read more news coverage from the 2017 AMA Annual Meeting.

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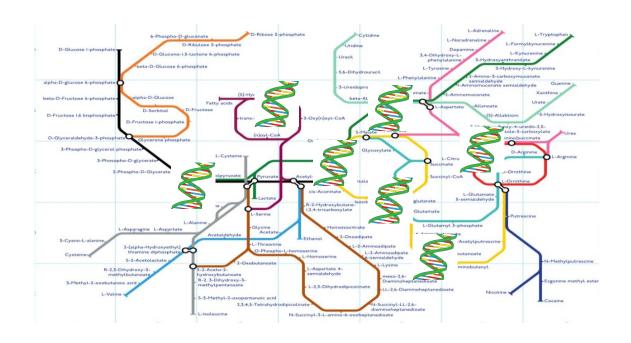
Gene-guided Intervention

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.

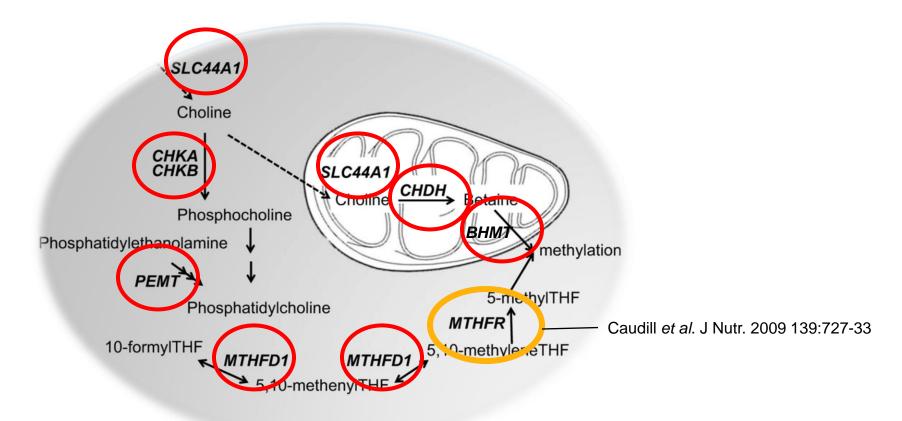


Moving from one SNP to complex multiple SNPs involved in metabolic pathways.





Common SNPS alter sensitivity to low choline



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



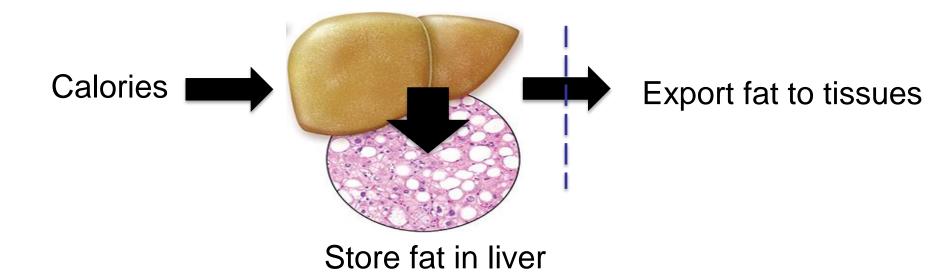
Choline deficiency presents differently – Why?



Of people who develop organ dysfunction

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

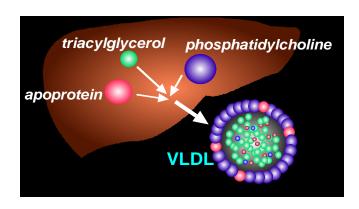




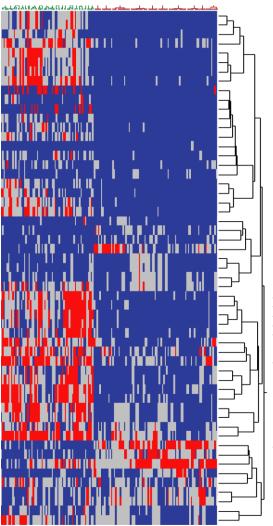
Choline needed for exporting fat from liver.



NAFLD predicted by choline SNPs







0 1 Variant alleles 2

SLC44A1_rs7018875 SLC44A1_rs10820799 CHKB rs7238 SLC44A1_rs193008 SLC44A1_rs328006 SLC44A1_rs443094 SLC44A1_rs440290 MTHFD1_rs10135928 PEMT_rs12103822 MTHFR rs7525338 MTHFR_rs868014 SCD_rs12247426 CHDH rs7634578 PCYT1B rs4898190 CHDH rs 2289209 CHKB rs 1557503 FADS2 rs2526678 PEMT_rs13342397 PEMT rs 16961845 PEMT_rs7214988 PEMT_rs8068641 PEMT_rs1109859 PCYT1A_rs1580820 MTHFR_rs2066471 CHDH_rs12676 SCD_rs11557927 SCD_rs11599710 SCD_rs2167444 SCD_rs7849 ABCB4 rs1149222 ABCB4 rs 31672 ABCB4_rs2071645 ABCB4 rs4148811 ABCB4_rs9655950 CHKB_rs1557502 FADS2_rs526126 APOC3 rs 2854117 CHDH_rs4563403 CHDH_rs 881883 CHDH_rs4687591 CHDH_rs6807783 PEMT_rs4479310 PEMT_rs7946 MTHFR_rs4846048 MTHFR_rs4846052 ABCB4 rs 1202283 CHKB_rs470117 PEMT_rs936108 MTHFR_rs1801133 STAT3 rs 9891119 PNPLA3 rs2281135 PNPLA3_rs738409 PEMT rs 4244593 PEMT_rs6502603

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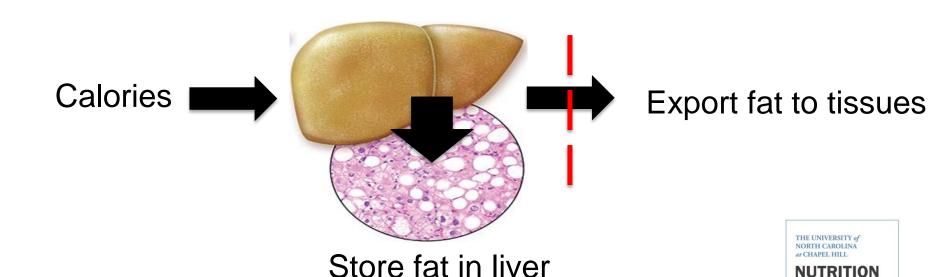
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More than just choline

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

FASEB J. 2013 27:1674-89

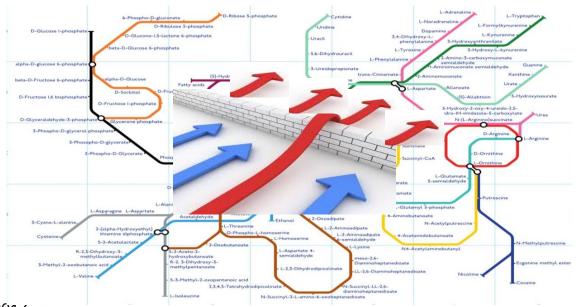
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Gene-guided Intervention

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.





Choline deficiency presents differently – Why?

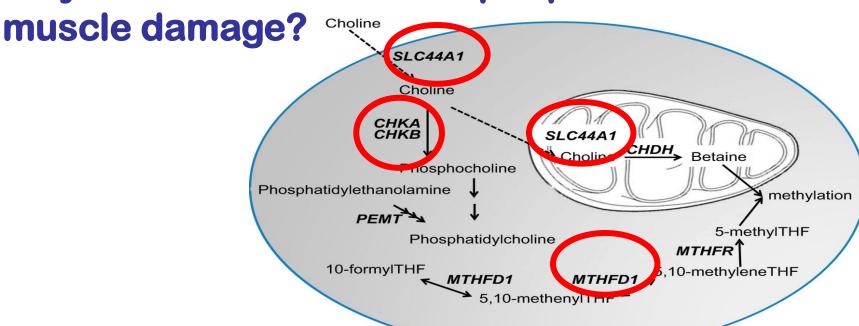


Of people who develop organ dysfunction

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



Why low choline in 10% of people results in



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)

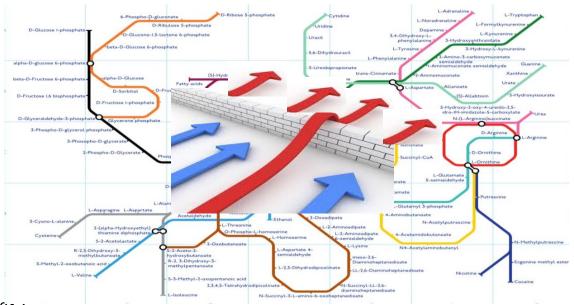
Marine officer candidates with high serum CK levels more often had the *MTHFD1* rs2236225 A allele than did men with normal CK levels (odds ratio 2.84, p=0.05).



Gene-guided Intervention

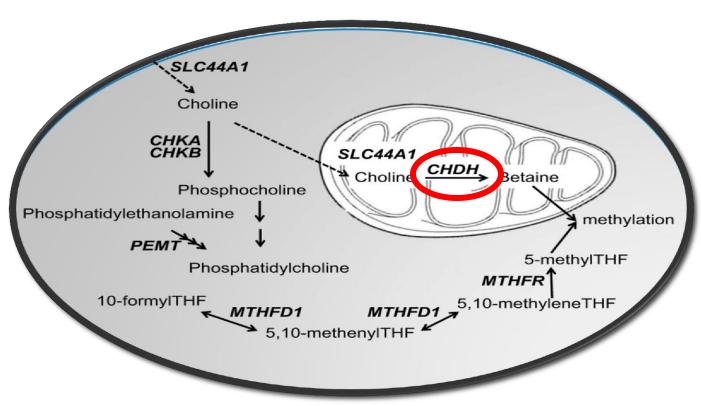
Problem: People with SNPs in multiple genes are at greater risk for developing rhabdomyolysis when they exercise

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





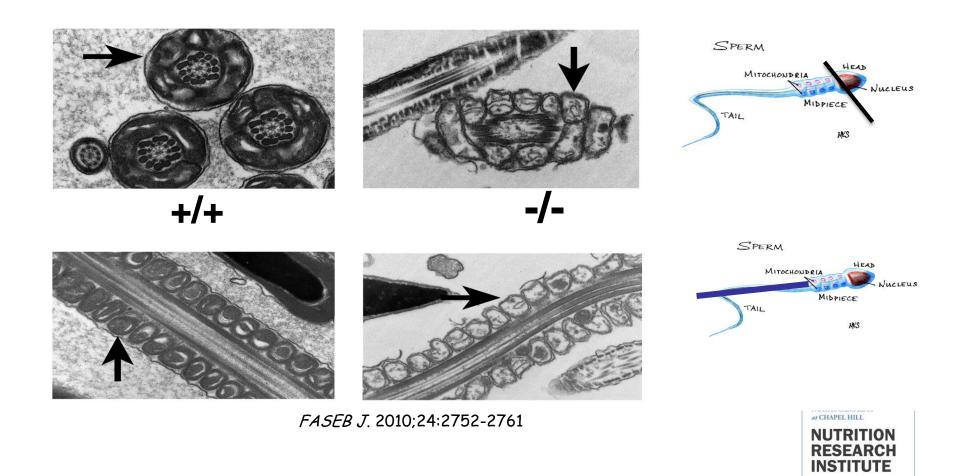
SNPS and sperm dysfunction



FASEB J. 2014 28:2970-8.

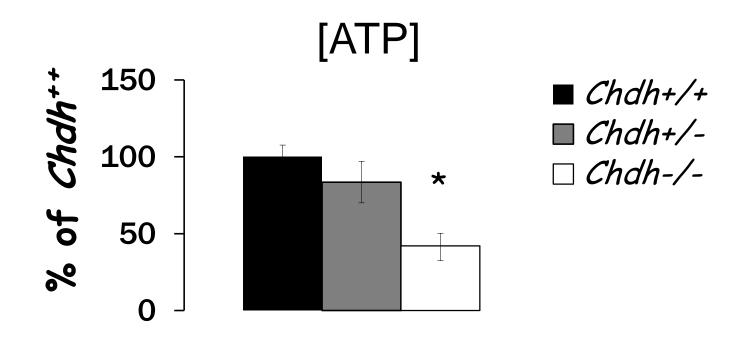


Deletion of *Chdh* results in dysmorphic mitochondria



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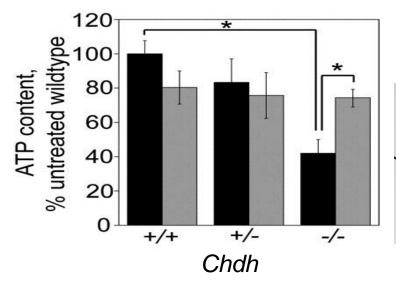
Deletion of *Chdh* results in low ATP

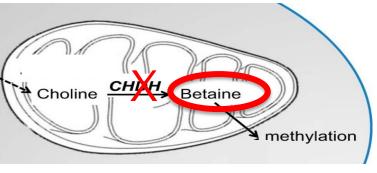


FASEB J.2010;24:2752-2761



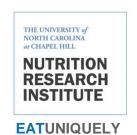
Betaine restores ATP





No betaine +betaine

FASEB Journal 24:2752-2761, 2010

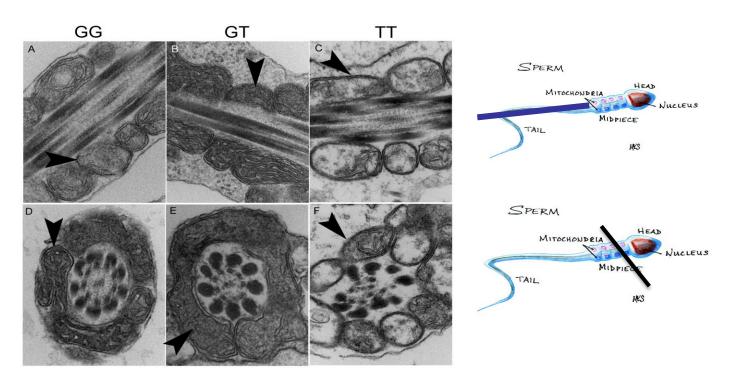


Men with CHDH rs12676 G233T





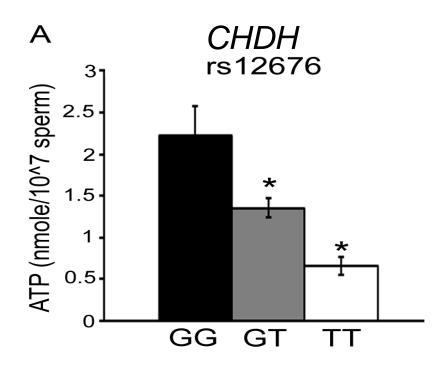
CHDH rs12676 G233T have dysmorphic mitochondria



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



CHDH rs12676 G233T have low ATP



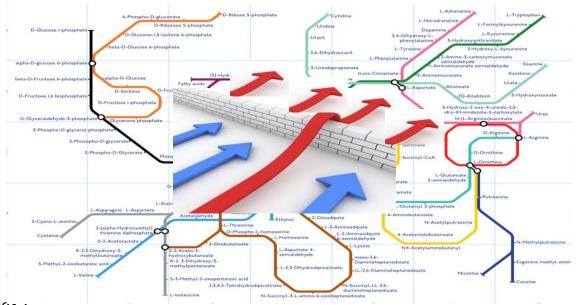
PLoS One. 2012;7:e36047. doi: 10.1371/journal.pone.0036047



Gene-guided Intervention

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

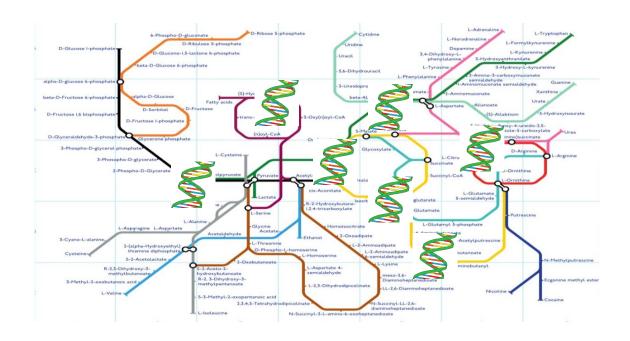
Intervention: Delivers metabolites that bypass blocks in these specific pathways.

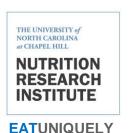




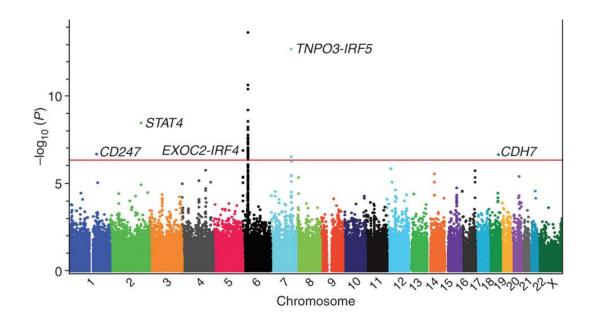
Future developments:

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





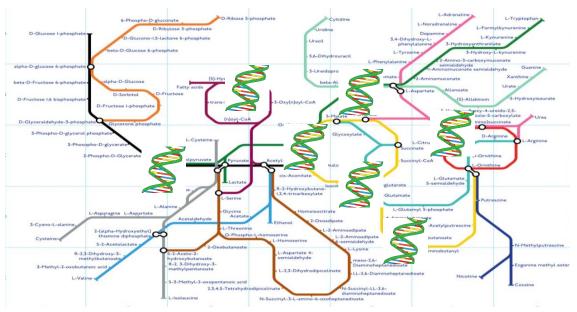
Including Diet intake (diet challenges) in GWAS studies



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



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. THE UNIVERSITY of MORTH CAROLINA (#CHAPPEL HILL.



Thank you



N. Surzenko Y. Wang



I. Trujillo

E. Pjetri











A. Johnson



K-A. da Costa



M. Spencer



S. Goodson



W. Sha



Y-W. Teng



L. Fischer



E. Yen



X. Zhu





M. Niculescu



K. Corbin



C. Craciunescu



J. Song





M. Mehedint



M. Resseguie



H-M. Hwang



X. Zhou



D. Lupu



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Funding: NIH (NIDDK, ODS, NIA), USDA, Bill & Melinda Gates Fdn, Nestle



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