WORKSHOP

Nutrigenomics, Methylation and RNA Based Nutrients

Dr. Amy Yasko
<table>
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<td>V158M</td>
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<td>VDR</td>
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<td>VDR</td>
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<tr>
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Genetic Testing as a Way to Evaluate the Genetic Contribution of Multifactorial Disease.

Custom nutrigenomic test for methylation cycle.

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What is Methylation?
Methylation
Methyl groups – CH3

Bound to DNA, enzymes, vitamins
The Importance of Methylation
Methylation

- DNA synthesis
  - Megaloblastic anemia
  - T cells
  - Intestinal mucosa
- Involved in DNA regulation
  - Host
  - Viral
- Myelination and pruning
- Proper immune response to i.e. TB
- Membrane fluidity, phospholipid methylation
- Enzymatic reactions requiring methylation
  - Melatonin
  - Neurotransmitter levels: dopamine, norepinephrine
  - Tryptophan methylation: serotonin,
Coenzyme Q$_{10}$

Ubiquinol (CoQH$_2$)

Semiquinone radical (CoQH$^\cdot$)

Ubiquinone (CoQ)
Melatonin

$N$-acetyl-$5$-methoxytryptamine

Serotonin

$5$-HT; $5$-hydroxytryptamine
SAMe is involved in the synthesis of:

- Creatine
- Methylcobalamin
- Phosphatidylcholine
- Coenzyme Q10
- Carnitine
- Methylation by SAMe is a critical step in the stabilization of many proteins including myelin.
The Methylation Cycle
"When the need is for energy and not for cysteine, homocysteine is metabolized to Alpha KG, NH3 and H2S."

Textbook of Biochemistry with Clinical Correlations, Devlin 2002
COMT

COMT is the enzyme that inactivates dopamine and norepinephrine by adding a methyl group to these compounds.

- COMT has an allelic variation with high activity, which decreases dopamine
- COMT has an allelic variation with low activity, leads to less of a decrease of dopamine
In the case of COMT the amino acid change is from a valine to a methionine. This is what is being tested for in the COMT genetic test. The labs are able to look at the DNA to determine which amino acid your version of COMT has. If you have the version with a methionine in it is written as COMT + meaning the genetic test is positive for the methionine version. If the result is COMT- it means that you do not have methionine in that spot of the enzyme and have valine there instead. Since the valine in that spot is considered the “norm” the methionine represents the variation, so it is + for a variation being present.

The form of the COMT with the variation (the methionine in it at a particular location) is a less efficient form of the enzyme. When the methionine is present it does not do as good a job of breaking down the dopamine. So an individual with the COMT+ will not break dopamine down as easily. An individual with COMT-(with the valine in that spot) will break dopamine down more efficiently.

The reason that we have two ++ or two - - or + - is that we all have two copies of the DNA for the COMT enzyme; one from each parent. Another way to represent COMT + + is as COMT met/met. Another way to represent COMT - - is as COMT val/val.
COMT ++

Tryptophan → Tyrosine

BH4

ALUM

DHPR

BH2

Serotonin

MAO A

HIAA

Dopamine

SAMe

NorEp

COMT → SAH

HVA

COMT → SAH

VMA
High Dopamine Foods

- Alcoholic beverage (some, not all alcohol)
- Homemade yeast breads
- Crackers containing cheese
- Sour cream
- Bananas
- Red plums
- Avocados
- Figs
- Raisins
- Aged game
- Liver
- Canned meats
- Yeast extracts
- Commercial meat extracts
- Stored beef liver
- Chicken livers
- Salami
- Sausage
- Aged cheese (including Blue, Boursalt, Brick, Brie, Camembert, Cheddar, Colby, Emmental, Gouda, Mozzarella, Parmesan, Provolone, Romano, Roquefort, and Stilton)
- Salted dried fish (herring, cod), pickled herring
- Italian broad beans
- Green bean pods
- Eggplant
- Yeast concentrates or products made with them
- Marmite
- Soup cubes
- Commercial gravies - anything with soy sauce, and an protein that has not been stored properly or has some degree of spoilage (i.e., all but those that have been freshly prepared).
High Tryptophan Foods may increase Serotonin

- Spirulina (seaweed)
- Soy Nuts
- Chicken Liver
- Pumpkin Seeds
- Turkey
- Chicken
- Tofu

- Watermelon Seeds
- Almonds
- Peanuts
- Brewer’s Yeast
- Cottage Cheese
- Milk
- Yoghurt
"When the need is for energy and not for cysteine, homocysteine is metabolized to Alpha KG, NH3 and H2S."

Textbook of Biochemistry with Clinical Correlations, Devlin 2002

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Vitamin D and Dopamine


**Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells.**

Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK.

Laboratory of Molecular Neurobiology, Barrow Neurological Institute, Phoenix, AZ 85013, USA.

We examined expression of the 1,25-dihydroxyvitamin D3 [1,25-(OH)2 D3] receptors in chromaffin cells of the adrenal medulla and the effects of 1,25(OH)2 D3 on expression of the tyrosine hydroxylase (TH) gene. Accumulation of 1,25(OH)2 D3 in the nuclei of adrenal medullary cells, but not in the adrenal cortex, was observed in mice intravenously injected with radioactively labeled hormone. 1,25(OH)2 D3 produced concentration-dependent increases in the TH mRNA levels in cultured bovine adrenal medullary cells (BAMC). The maximal increases (2-3-fold) occurred at 10(-8) M 1,25(OH)2 D3. Combined treatment with 1,25(OH)2 D3 and 20 microM nicotine had no additive effect on TH mRNA levels suggesting that transsynaptic (nicotinic) and vitamin D (hormonal) stimulation of TH gene expression are mediated through converging mechanisms. Induction of TH mRNA by 1,25(OH)2 D3 was not affected by calcium antagonist TMB-8. By increasing expression of the rate limiting enzyme in the catecholamine biosynthetic pathway, 1,25-(OH)2 D3 may participate in the regulation of catecholamine production in adrenal chromaffin cells. This regulation provides mechanisms through which 1,25(OH)2 D3 may control response and adaptation to stress.
• High Vitamin D is associated with lower rates of osteoarthritis

• Previous study showed that the absence of the Taq and Bsm sites were associated with lower levels of osteoarthritis

• Implies that lack of Taq and Bsm lead to higher levels of Vitamin D

• High Vitamin D increases dopamine

• Fits with observation that Bsm - - and Taq - - may mitigate other mutations in autism severity

• Fits with observation that Bsm - - and Taq - - COMT + + children are the most sensitive to dopamine and methyl groups
Abstract
Previous studies have suggested that lead exposure may be associated with increased risk of amyotrophic lateral sclerosis (ALS). Polymorphisms in the genes for -aminolevulinic acid dehydratase (ALAD) and the vitamin D receptor (VDR) may affect susceptibility to lead exposure. We used data from a case-control study conducted in New England from 1993 to 1996 to evaluate the relationship of ALS to polymorphisms in ALAD and VDR and the effect of these polymorphisms on the association of ALS with lead exposure. The ALAD 2 allele (177G to C; K59N) was associated with decreased lead levels in both patella and tibia, although not in blood, and with an imprecise increase in ALS risk [odds ratio (OR) = 1.9; 95% confidence interval (95% CI), 0.60-6.3]. We found a previously unreported polymorphism in ALAD at an Msp1 site in intron 2 (IVS2+299G>A) that was associated with decreased bone lead levels and with an imprecise decrease in ALS risk (OR = 0.35; 95% CI, 0.10-1.2). The VDR B allele was not associated with lead levels or ALS risk. Our ability to observe effects of genotype on associations of ALS with occupational exposure to lead or with blood or bone lead levels was limited. These findings suggest that genetic susceptibility conferred by polymorphisms in ALAD may affect ALS risk, possibly through a mechanism related to internal lead exposure. Key words: -aminolevulinic acid dehydratase, amyotrophic lateral sclerosis, genetic susceptibility, lead, vitamin D receptor. Environ Health Perspect 111:1335-1339 (2003). doi:10.1289/ehp.6109 available via http://dx.doi.org/ [Online 1 April 2003]
A deficiency in dihydrobiopterin reductase or dihydrobiopterin synthetase leads to hyperphenylalaninemia and decreased synthesis of catecholamines and serotonin.
Glutathione depletion in nigrostriatal slice cultures: GABA loss, dopamine resistance and protection by the tetrahydrobiopterin precursor sepiapterin.

Gramsbergen JB, Sandberg M, Moller Dall A, Kornblit B, Zimmer J.

Anatomy and Neurobiology, Institute of Medical Biology, SDU-Odense University, Winsloewparken 21, DK-5000 C Odense, Denmark. jbg@imbmed.ou.dk

Dopaminergic neurons in culture are preferentially resistant to the toxicity of glutathione (GSH) depletion. This effect may be due to high intrinsic levels of tetrahydrobiopterin (BH(4)). Here we studied the effects of manipulating GSH and/or BH(4) levels on selective neurotoxicity in organotypic nigrostriatal slice cultures. Following treatments with L-buthionine sulfoximine (BSO, 10-100 microM, 2 days exposure, 2 days recovery), either alone or in combination with the BH(4) precursor L-sepiapterin (SEP, 20 microM), or the BH(4) synthesis inhibitor 2,4-diamino-6-hydroxypyrimidine (DAHP, 5 mM), toxic effects were assessed by HPLC analysis of medium and tissues, cellular propidium iodide (PI) uptake, lactate dehydrogenase (LDH) efflux, as well as stereological counting of tyrosine-hydroxylase (TH) positive cells. Thirty micromolar BSO produced 91% GSH and 81% GABA depletion and general cell death, but no significant effect on medium homovanillic acid (HVA) or tissue dopamine (DA) levels. SEP prevented or delayed GABA depletion, PI uptake and LDH efflux by BSO, whereas DAHP in combination with BSO caused (almost) complete loss of medium HVA, tissue DA and TH positive cells. We suggest that under pathological conditions with reduced GSH, impaired synthesis of BH(4) may accelerate nigral cell loss, whereas increasing intracellular BH(4) may provide protection to both DA and GABA neurons.
Preferential resistance of dopaminergic neurons to the toxicity of glutathione depletion is independent of cellular glutathione peroxidase and is mediated by tetrahydrobiopterin.

Nakamura K, Wright DA, Wiatr T, Kowlessur D, Milstien S, Lei XG, Kang UJ.

Department of Neurology, University of Chicago, IL 60637, USA.

Depletion of glutathione in the substantia nigra is one of the earliest changes observed in Parkinson's disease (PD) and could initiate dopaminergic neuronal degeneration. Nevertheless, experimental glutathione depletion does not result in preferential toxicity to dopaminergic neurons either in vivo or in vitro. Moreover, dopaminergic neurons in culture are preferentially resistant to the toxicity of glutathione depletion, possibly owing to differences in cellular glutathione peroxidase (GPx1) function. However, mesencephalic cultures from GPx1-knockout and wild-type mice were equally susceptible to the toxicity of glutathione depletion, indicating that glutathione also has GPx1-independent functions in neuronal survival. In addition, dopaminergic neurons were more resistant to the toxicity of both glutathione depletion and treatment with peroxides than nondopaminergic neurons regardless of their GPx1 status. To explain this enhanced antioxidant capacity, we hypothesized that tetrahydrobiopterin (BH(4)) may function as an antioxidant in dopaminergic neurons. In agreement, inhibition of BH(4) synthesis increased the susceptibility of dopaminergic neurons to the toxicity of glutathione depletion, whereas increasing BH(4) levels completely protected nondopaminergic neurons against it. Our results suggest that BH(4) functions as a complementary antioxidant to the glutathione/glutathione peroxidase system and that changes in BH(4) levels may contribute to the pathogenesis of PD.
DHPR ++

Diagram of the DHPR pathway showing the conversion of tryptophan and tyrosine into serotonin and dopamine through the intermediates BH2 and BH4, with the involvement of DHPR and MTHFR enzymes.
MTHFR C677T

Krebs's Cycle
- Fumarate
  - Aspartate

Arginine
- Ornithine
- UREA
  - Ammonia
  - OTC

Ornithine
- Aspartate
- Citrulline + NO

Hypoxanthine
- Guanido Ac
- Creatine
  - Creatinine

Cystathionine
- Cysteine

Homocysteine
- Methionine
  - MTR
  - BHMT
  - TMG

Methionine
- DNA, RNA
  - Methylation
  - Protein, lipids

5 Methyl THF
- THF
- 5, 10 Methylene THF

Dopamine
- MAO A
- Serotonin

NorEp
- SAMe
- SAH

SAMe
- THF
- Methionine

BH4
- NOS
- LEAD

GABA
- gaba

Glutamate
- GAD

Neuronal Damage

Peroxynitrite
- SOD

G6PDH

Angiotensin I
- ACE

Angiotensin II

Sulfite
- SUOX

Sulfate
- cortisol

Textbook of Biochemistry with Clinical Correlations, Devin 2002

"When the need is for energy and not for cysteine, homocysteine is metabolized to Alpha KG, NH3 and H2S."

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MTR ++
MTRR and MTR ++

Purines

5, 10 Methylene THF

MTHFR

MTR

THF

dUMP

5 Methyl THF

Methionine

MAT

SAMe

MTRR

B12

BHMT

DMG

TMG

SAH

Homocysteine

AHCY
CBS C699T++

CBS

cystathionine

Cysteine + αKG → AMMONIA

High Cysteine → taurine
Low Cysteine → glutathione

Alpha KG + H2S + NH3

sulfite → SUOX → sulfate

cortisol → ACE → Angiotensin II

Angiotensin I → G6PDH
The essentiality of sulfur is closely related to nitrogen metabolism: a clue to hyperhomocysteinaemia

N and S metabolisms are closely interwoven throughout both the plant and animal kingdoms. The essentiality of S relates to its participation in the structure of S-containing amino acids (SAA), to its inclusion in many sulfonated molecules, and to a myriad of metabolic and catalytic reactions of vital importance. Methionine (Met) is the indispensable SAA supplied by food proteins and its plasma homeostasis is achieved via a number of highly efficient regulatory mechanisms. In all conditions characterized by a negative body protein balance such as in dietary restriction or cytokine-induced hypercatabolic losses, N and S endogenous pools manifest parallel tissue depletion rates. Adaptive conservation of N and S body stores is reached by a functional restraint of the trans-sulfuration cascade, through the depression of cystathionine -synthase activity. As a result, upstream accumulation of homocysteine favors its re-methylation conversion to Met which helps maintain metabolic pathways of survival value.
Inducing a “topor like” state with hydrogen sulfide gas. The gas competes with oxygen in mitochondria, slowing the metabolic activity.

Topor is an extreme state of metabolic slowdown in which the heart rate drops, breathing slows and body temperature plunges.
MTHFR A1298C and CBS C699T
A1298C/ CBS/ ↑Protein

- Increased ammonia puts strain on the urea cycle.
- Decreases BH4.
- May either generate excessive Nitric Oxide or not enough NO.
- Also generates peroxy nitrite and superoxide. Excess superoxide in turn affects SOD.
Ammonia toxicity

- Disorientation, “brain fog”, confusion
- Flapping tremors of extended arms
- Hyperactive reflexes
- Activation of N-methyl-D-aspartate receptors leading to glutamate excitotoxicity
- Tremor of the hands
- Paranoia, panic attacks
- Memory loss
- Hyperventilation (caused by respiratory alkalosis of high ammonia levels that stimulate the respiratory center; respiratory alkalosis is often associated with decreased CO2)
- CNS toxicity affecting glial and nerve cells a, leading to altered CNS metabolism and function.
Complicating mutation
The urea cycle is an endergonic process that ultimately requires the hydrolysis of 3 ATP's for each molecule of urea produced.

In the first reaction, which occurs in mitochondria, bicarbonate (HCO₃⁻) is combined with NH₄⁺ to form carbamoyl phosphate.

http://www.lander.edu/flux/301_aminoacid_catabolism.htm

Relationship to Krebs Cycle

In the first reaction, which occurs in mitochondria, bicarbonate (HCO₃⁻) is combined with NH₄⁺ to form carbamoyl phosphate.

http://www.lander.edu/flux/301_aminoacid_catabolism.htm
Changes in values on biochemical tests may reflect pathways that have been impaired by mutations, leading to increases in intermediates in pathways.
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| Beta-alanine           | 69     | < 12            |        |      |      |      |        |

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With decreased ammonia, arginine from the urea cycle is available to produce creatinine. This can cause increases in asparatate. Asparate can then feed into the Krebs cycle to increase the level of oxaloacetate. Aspartate can also result in elevated beta alanine. Beta alanine can lead to increased levels of carnosine and anserine.
Elevated creatinine and elevated aspartate due to decreased ammonia/urea cycle activity and decreased available methyl groups due to detoxification can lead to increased beta alanine.

- **Uracil**
- **Thymidine**
- **L-Aspartate**
- **β-Alanine**
- **Histidine**
- **Carnosine**
- **(R)-Pantothenate**
- **(R)-Pantothenate and CoA biosynthesis**
- **Aspartate Metabolism**
- **Anserine**
Increased levels of phenylalanine as a result of decreased BH4 can lead to increases in hippurate.
As creatinine decreases sarcosine can be seen to increase.
Knowing the nutrigenomic profile helps to ascertain if increased levels of intermediates are a result of

- Buildups due to mutations
- Result of other causes
How can you address these nutrigenetic issues?
Relationship between specific genetic mutations and biochemical pathways and we can use this knowledge to address these mutations
Example: support for methylation cycle mutations

**Methylation Cycle Supplementation**

- ¼ Folapro
- ¼ Intrinsic B12
- ¼ Nucleotides
- Methylation Support RNA
- TMG and /or phosphatidyl serine
- Sublingual B12 and /or B12 injections
  - COMT + + : hydroxy cobalamin
  - COMT - -: methyl cobalamin
  - Regardless of COMT status: cyano cobalamin (eyes)
- Methionine
  - SAMe for COMT - -
  - Methionine COMT + +
- Optional methyl donors for COMT - - and COMT + -
  - MSM, TMG, DMG, curcumin, methyl B12, melatonin, FGF, caffeinated tea
DNA for testing
RNA for balancing
Knowledge is power. Armed with this knowledge and genetic profile analysis we can select precise natural RNA formulas that will aid in cell-to-cell communication to help to address the genetic susceptibilities that are involved in a variety of health conditions. (Stress, Health Foundation, Heart Support, Methylation Support, Nerve Calm, Mood S, Mood D, Mood Focus, Respiratory Support, Brain Support, CSF Support, Lipid Support, Kidney Support, Healthy Microbial Balance, Organ Support, Bone Support and ProLongevity RNA NutriSwitch™ Formulas among others). For while we cannot change our genes, we can help to enhance the expression of these genes.

www.longevityplus_rna.com
**ProLongevity NutriSwitch RNA**

Female, 72

<table>
<thead>
<tr>
<th></th>
<th>Before Prolongevity</th>
<th>After Prolongevity</th>
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</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>425</td>
<td>242</td>
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<tr>
<td>Total Cholesterol</td>
<td>218</td>
<td>185</td>
</tr>
<tr>
<td>Glucose</td>
<td>152</td>
<td>69</td>
</tr>
<tr>
<td>HDL</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>LDL</td>
<td>131</td>
<td>101</td>
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</table>
# ProLonegivity NutriSwitch RNA

**Male, 68**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Triglycerides</td>
<td>170*</td>
<td>141</td>
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<tr>
<td>Total Cholesterol</td>
<td>191</td>
<td>164</td>
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<tr>
<td>Glucose</td>
<td>132</td>
<td>102</td>
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<tr>
<td>HDL</td>
<td>39</td>
<td>36</td>
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<tr>
<td>LDL</td>
<td>125</td>
<td>100</td>
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</table>

*Average of prior levels*
ProLongevity NutriSwitch RNA
Male, 43

<table>
<thead>
<tr>
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<th>Before Prolongevity</th>
<th>After Prolongevity</th>
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</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>356</td>
<td>208</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>230</td>
<td>170</td>
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<tr>
<td>Glucose</td>
<td>93</td>
<td>93</td>
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<tr>
<td>HDL</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>LDL</td>
<td>114</td>
<td>83</td>
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</tbody>
</table>
Effect of Lipid Support RNA NutriSwitch on LDL

43 yr. old Male, E.Y.

- Nov. 6, 2003
- Nov. 19, 2003
- Dec. 5, 2003
- Jan. 14, 2004
- Jan. 23, 2004
- May 21, 2004
Effect of **Lipid Support RNA NutriSwitch** on Cholesterol

43 yr. old Male, E.Y.

![Bar chart showing total cholesterol levels over time](chart.png)

- Nov. 6, 2003: 300
- Nov. 19, 2003: 275
- Dec. 5, 2003: 250
- Jan. 14, 2004: 225
- Jan. 23, 2004: 200
- Apr. 1, 2004: 175
- May 21, 2003: 150

**Total Cholesterol**
Effect of Lipid Support RNA NutriSwitch on Cholesterol

68 yr. old Male, F.R.

Chol.
Safety of NutriSwitch Lipid Support

[Bar graph showing ALT and AST levels with and without Lipid Support]

- With Statin Drugs:
  - ALT: 70
  - AST: 40

- With Lipid Support RNA NutriSwitch:
  - ALT: 30
  - AST: 30

Normal Range: 40
Effect of Lipid Support RNA NutriSwitch Formula on Triglycerides

68 yr. old Male, F.R.
Effect of Lipid Support RNA NutriSwitch Formula on Triglycerides
46 yr. old Male, D.C.

Triglycerides

Glucose Support RNA NutriSwitch
D.A., Male, Age 80

Glucose Support RNA NutriSwitch

Fasting Glucose
Effect of Nerve Calm RNA NutriSwitch on Excitotoxins

Seizure Activity

Avg. # Seizures/Day
Heal Your Body Naturally:

The Power of RNA

By Dr. Amy Yasko and Dr. Garry Gordon

A layman’s guide to RNA and its use for optimal health.

RNA

Boston Conference, August 2004, DVD
Phoenix Conference, April 2005, DVD
Heal Your Body Naturally, book
RNA Educational Starter Package

www.holistichealth.com
www.holisticheal.com
www.autismanswer.com Parents chatroom
www.longevityplus-rna.com
Factors Contributing to Autism

Putting It All Together Parents Weekend DVD
Boston Conference, August 2004 DVD
The Puzzle of Autism, book
Dr. Amy’s Supplement Video
Autism Educational Starter Package

www.holistichealth.com
www.holisticheal.com
www.autismanswer.com Parents chatroom
www.longevityplus-rna.com
**Nutrigenomics**

Boston Conference, August 2004, *DVD*

Genetic ByPass, *book*

Genetic Educational Starter Package

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- www.holistichealth.com
- www.holisticheal.com
- www.autismanswer.com *Parents chatroom*
- www.longevityplus-rna.com
Additional Resources
Specific information about supplements can be obtained at www.holisticheal.com
Dr. Amy’s personal website is www.holistichealth.com
Dr. Amy answers questions at www.autismanswer.com

Videos/DVDs that are divided by topic:
  - Glutamate and Gaba
  - Neurological Inflammation, Video or DVD
  - Virus, Metals, Methylation
    Austin Conference, November 2004 DVD
    Phoenix Conference, April 2005 DVD
  - Factors Contributing to Autism
    Putting It All Together Parents Weekend, Video or DVD
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