“Autism” and a Family:
Perspectives of a Parent & Patient

PCORI EAIN-3885 – April 7th

Presenter: Seth Bittker

Introduction – Portrait of a family

- **Boy:** 10 years old. **Autism** diagnosis when younger. Regressive. Currently "high functioning". Likes bonding. Great memory. Slow processing. Very bad handwriting.
- **Sister:** 8 years old. Modest **OCD**.
- **Father (me):** 47 years old. Polyneuropathy, insomnia, headaches, digestive issues, and occasional essential tremor.
- **Paternal aunt:** 45 years old. Arthritis. Polyneuropathy. Headaches and fatigue.
- **Paternal grandmother:** 73 year old. Arthritis like condition. Bones break easily. Pains in joints.

Genetic testing

- **Boy:**
  - **Autism panel** ~ 2010: nothing of significance
- **Paternal aunt:**
  - **Illumina Rare Disease Whole Genome Sequencing**
    - "C" deletion at position 3106 in the **16S gene** (mitochondrial DNA)
- **Father (me):**
  - **Baylor Whole Exome Sequencing**
    - Two separate single recessive gene defects associated with **Charcot Marie Tooth** – supposedly as these genes are recessive having one bad copy of each is of no medical significance
  - **23andme with Prometheas**
    - Two separate uncommon polymorphisms of **STAT4** associated with lupus
    - Missing **CNV** on chromosome 6 associated with **vascular issues**
    - "Bad" polymorphisms associated with **Cystathionine Gamma Lyase**, **TNF-alpha**, **MTHFR**

Trying supplements for autism* (n=1)

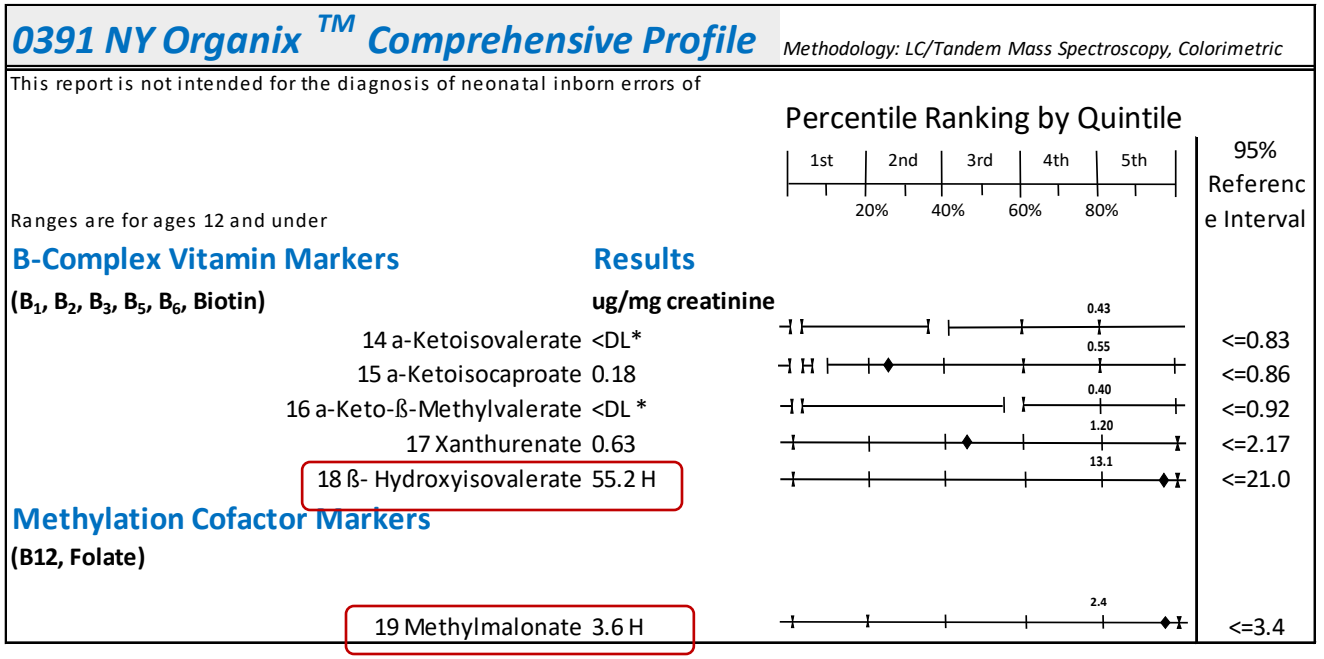
Observation with my son

Supplement	Double blind trial	Effect	In schedule
1. Methylcobalamin	Hendren, 2016	Good	Yes-oral
2. Folinic	Frye, 2016	Good (Methylfolate)	Yes-oral
3. Suforaphane	Singh, 2014	Bad	No
4. N-acetyl-cysteine	Hardan, 2012	Bad	No
5. Acetyl-l-carnitine	Fahmy, 2013	Bad	No
6. TTFD-thiamine derivativ	Lonsdale (not Db), 2002	Untested	No
7. Benfotiamine	None	Good	Yes
8. Biotin	None	Good	Yes
9. Epsom salt baths	None	Good	Rarely
10. Vitamin D	None validated	Very Bad	No
11. Vitamin K	None	Probably Good	Yes
12. Carotenoids	None	Good	Yes
13. Olive oil capsules	None	Probably Good	Yes

What drives the effectiveness of various supplements in my son?

Genetics?

Select vitamin B related metabolites in my son



0391 NY Organix ™ Comprehensive Profile

Methodology: LC/Tandem Mass Spectroscopy, Colorimetric

This report is not intended for the diagnosis of neonatal inborn errors of

Ranges are for ages 12 and under

Percentile Ranking by Quintile: 1st | 2nd | 3rd | 4th | 5th (20% | 40% | 60% | 80%)

	Results	95% Reference Interval
B-Complex Vitamin Markers		
(B_1, B_2, B_3, B_5, B_6, Biotin)	**ug/mg creatinine**	
14 a-Ketoisovalerate	<DL*	<=0.83
15 a-Ketoisocaproate	0.18	<=0.86
16 a-Keto-ß-Methylvalerate	<DL *	<=0.92
17 Xanthurenate	0.63	<=2.17
18 ß- Hydroxyisovalerate	55.2 H	<=21.0
Methylation Cofactor Markers		
(B12, Folate)		
19 Methylmalonate	3.6 H	<=3.4

- "Modest" functional **deficiencies of biotin** (high beta-hydroxyisovalerate) and **cobalamin** (high methylmalonate).
- Biotin and methylcobalamin seem to help, but benfotiamine and methylfolate do as well.

What are the genetics of this?

Example: Vitamin D3 supplementation–*good or bad*?

TEST	IN RANGE	OUT OF RANGE	REFERENCE RANGE	UNITS	TEST LOC
Non-Fasting Specimen					
Abnormal Summary					
Complete Blood Count, with Differential					
Red Blood Count		4.31 L	4.50-6.20	Mil/uL	
MPV		12.9 H	9.4-12.5	fL	
Lymphocyte, Absolute		1.23 L	1.50-4.50	Thou/uL	
CD4/CD8 Cell Count with Ratio					
CD4+ T Cells (%)		51H	7-35	%	
Comprehensive Metabolic Panel					
Alkaline Phosphatase		39 L	45-128	U/L	
Aspartate Aminotrans (AST)		67 H	10-55	U/L	
Alanine Aminotrans (ALT)		137 H	10-55	U/L	
C3D Immune Complex		33 H			
Vitamin D, 25-Hydroxy		27 L	30-100	ng/mL	
Vitamin D, 1.25-Dihydroxy					
Vitamin D, 1.25 (OH) 2, Total		90 H			
Parvovirus B19 IgG/IgM EIA					
Parvovirus Ab B19, IgG		4.70 H	<0.90	EIA INDEX	
Haemophilus Influenza Type B Ab, IgG					
H. Influenza Type B Ab		0.22 L			
Mycoplasma pneumoniae Antibody, IgG, IgM					
M. pneumoniae Ab, AgG		3.90 H			

- According to many medical practitioners those who are “low” on 25-Hydroxy vitamin D should supplement with vitamin D orally.
- Yet in **my family** sometimes we are **low on 25-Hydrox vitamin D** and **high on 1,25-Dihydroxy vitamin D**. See my personal results above.
- Probably relatedly **me**, **my sister**, **my mother**, **my son**, and **my daughter** (I think) have all had our health adversely affected by incidents of ill advised vitamin D supplementation or fortification. **What are the genetics of this?**

Autism Research Connections–Interview Series – autismrc.com

- **Why?**
  - Wanted a forum for serious discussions on biochemistry & potential therapeutics for autism without dogma & voodoo.
- **Takeaways**
  - One or many autisms? Both
  - Huge obstacles to rigorous but practical research

Researcher Name	Topics Discussed
Dr. Rosemary Waring	Sulfation deficits in autism
Dr. Derrick Lonsdale	Thiamine deficiency and supplementation in autism
Dr. Robert L. Hendren	Over-the-counter therapies (methyl-B12, Omega-3s, Vitamin D) in autism
Dr. Richard E. Frye	Mitochondrial dysfunction, autoimmunity, and over-the-counter therapies (folinic acid) in autism

Online Parent Survey*

(potential postnatal risk factors for autism)

- **Objective:** Evaluate association of 5 environmental factors
- **Participants:**
  - **Cases:** parents of children with ASD
  - **Controls:** parents of children who do not have ASD

Postnatal Exposure

1. Decreased breastfeeding
2. Antibiotic use
3. Acetaminophen use
4. Decreased vitamin D consumption

Prenatal Exposure

1. Maternal folate supplementation

*** This is a project of INCITE at Columbia University, directed by Dr. Peter Bearman, and I am a consultant on the project.**

What do I hope to achieve here?

1. Get some ideas that might help me and my family
2. Share some of my perspectives that might help others
3. Help move science forward
4. Make connections with others

Genetic studies that might benefit my son (and my family)

1. What are the genetic factors which determine effectiveness of various supplements in autism?

2. What are the genetic factors which determine harmfulness of various supplements in autism?

3. What genetic factors contribute to low plasma free sulfate in autism?*

*** Adams, 2011: Plasma free sulfate in autism is on average 35% of controls (n=99, p value <0.00001)**

Perspective on autism genetics field

1. **Identifying genetic mutations with high penetrance**
   - Researchers have a pretty good handle on this, yet a lot more research seems to be going in this direction.
2. **Effect of high penetrance mutations on biochemistry**
   - Little systematic research on this.
3. **What combinations of low penetrance genetic polymorphisms are critical to causing dysfunction?**
   - There appears to be little research on this.
4. **Identifying which supplement / drug is likely to be effective with specific genetics?**
   - There is some research on this but a lot more is needed.
5. **Identifying which supplement / drug will do harm with specific genetics?**
   - There is some research on this but a lot more is needed.

How can EAIN 3885 help?

- Big autism genetic studies such as **SPARK** and **MSSNG** obtain a lot of genetic data but little data on biochemistry or effectiveness of potential therapeutics.

- So perhaps some part of **EAIN 3885 (AutGO)** could provide a forum where genetic data could be analyzed in conjunction with biochemistry and / or treatment effectiveness.

Thank you