Metabolomics and Psychiatric Disease: NextGen Frontiers in Pathophysiology and Treatment

Brain and Behavior Research Foundation

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(see acknowledgements)

Topics to be Covered

- Discussion of treatment refractory depression.
- A case report and case control study.
- New diagnostic and treatment approaches to treatment refractory depression.
- Future directions for our current work.

Metabolic Disorder and Psychiatric Disease

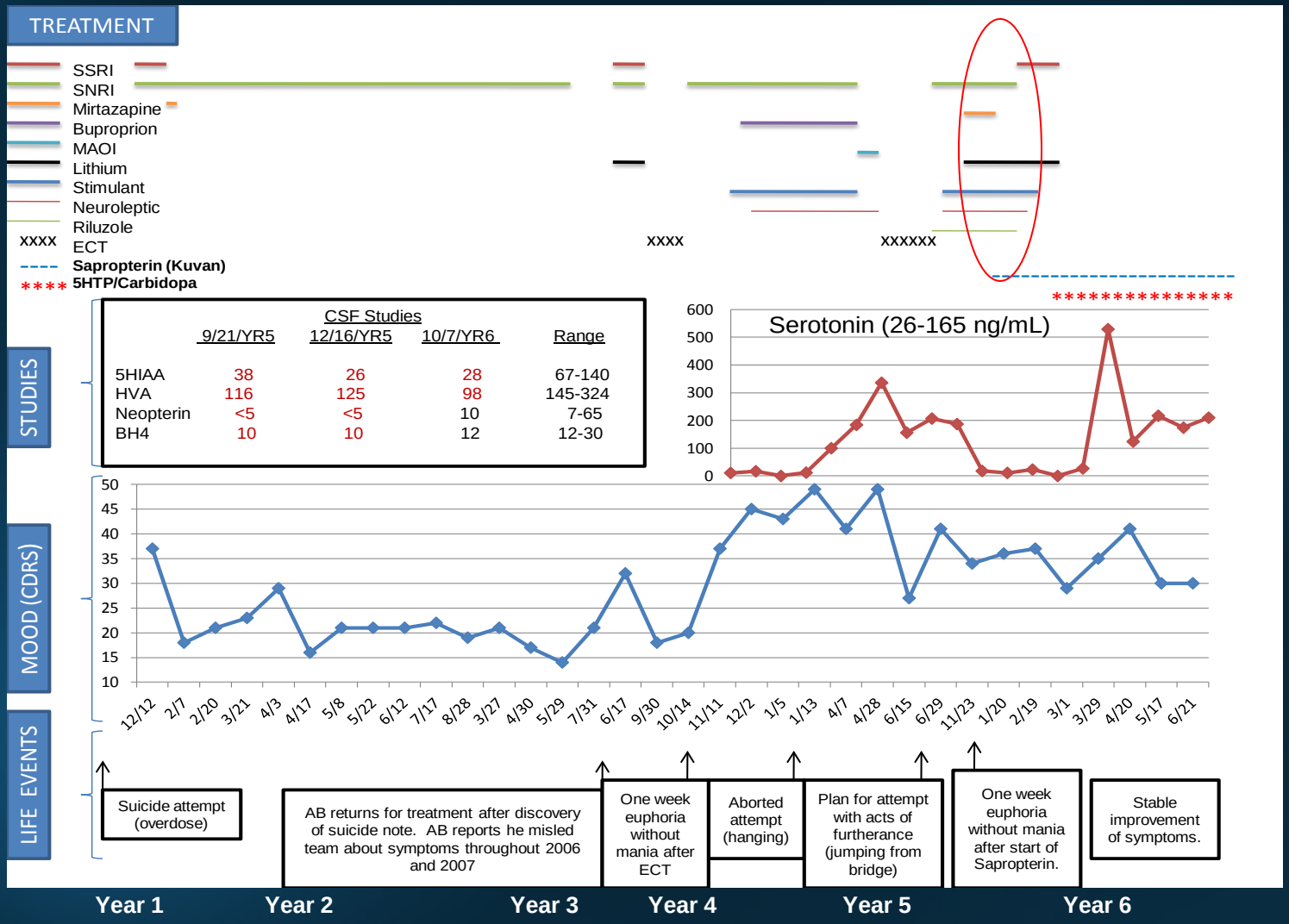
- Neuropsychiatric manifestations of IEMs are often identified presenting as emergencies, chronic fluctuating symptoms, or associated with mental retardation.

- Known psychiatric manifestations of intoxication syndromes, lipid storage disorders/oligosaccharidoses/ mucopolysaccharidoses, metal storage disorders.

- We hypothesized that milder central nervous system specific metabolic disorders may present later in life with isolated psychiatric symptoms.

Patient with treatment refractory depression and suicidal behavior

- Depression and self injury, age 11
- Suicide attempt age 14
- Age 15 suicide attempt 80 pills, discovered by chance, ICU stay.
- No response to available medications.
- Age 18, ECT with one week of response.
- Refused ECT due to non-response, 49 day hospital stay and evaluation for state hospitalization. No response of suicidal ideation despite aggressive treatment.
- *Permission provided to share this information, and case report published.*

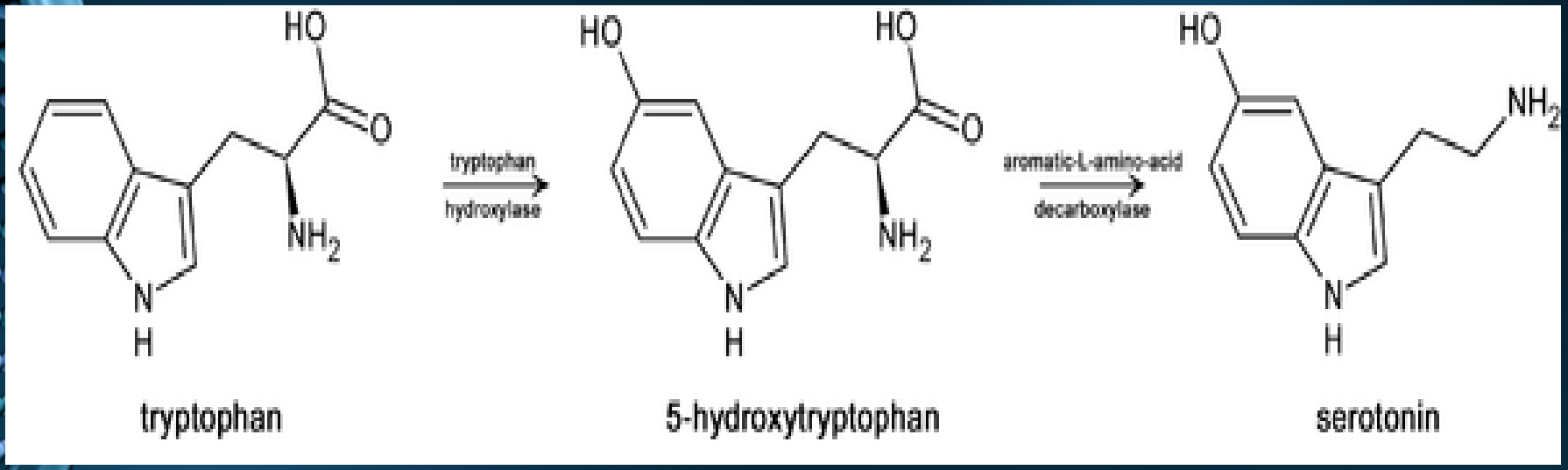


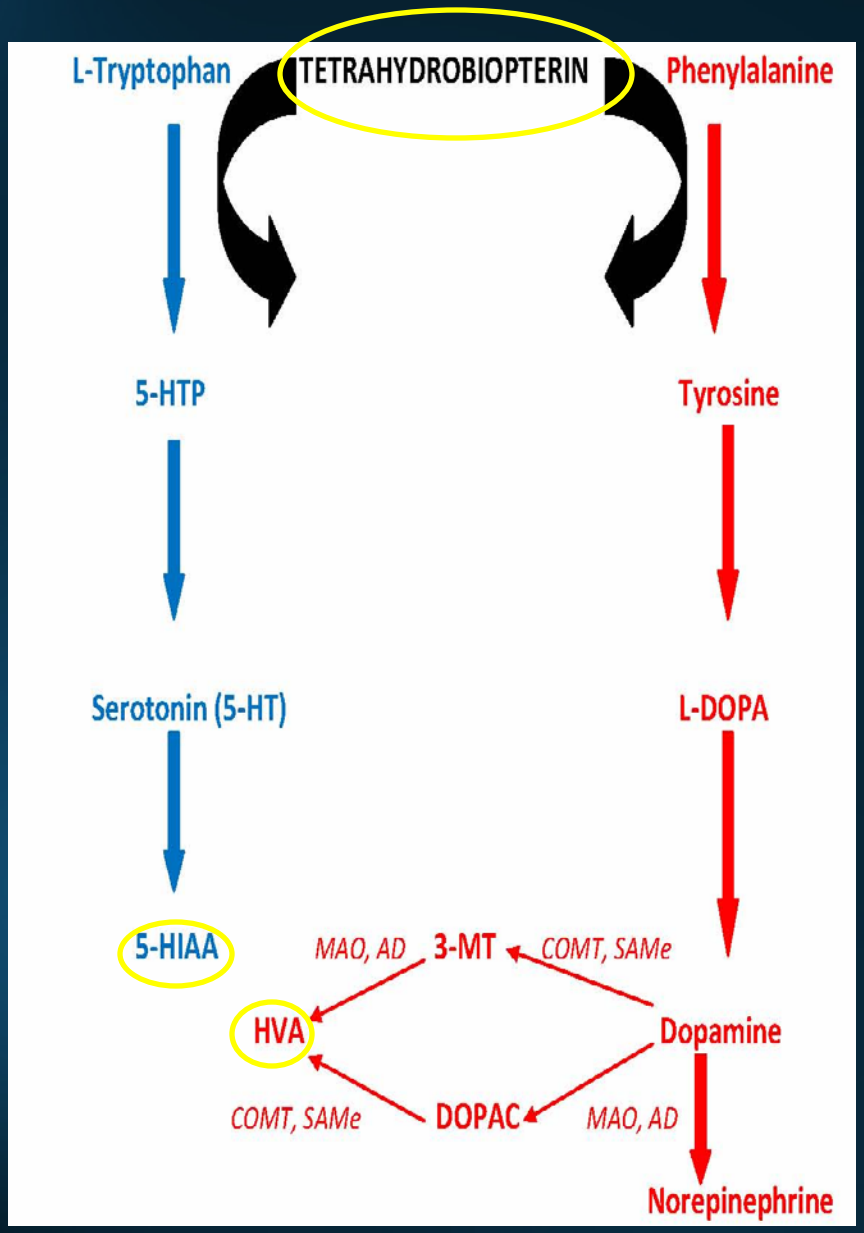
CDRS Children's Depression Rating Scale, SSRI Selective Serotonin Reuptake Inhibitor, SNRI Serotonin-Norepinephrine Reuptake Inhibitor, MAOI Monoamine Oxidase Inhibitor, ECT Electroconvulsive Therapy, 5HTP 5-Hydroxytryptophan, 5HIAA 5-Hydroxyindoleacetic Acid, HVA Homovanillic Acid, BH4 Tetrahydrobiopterin

Assessment

- We had exhausted available therapies and medication classes.
- In light of severe depression and suicide symptoms and discussion with cardiologist about aortic dilatation, spoke with medical genetics about evaluation for underlying disorder.
- Evaluation of blood, urine, and cerebrospinal fluid.
- CSF neurotransmitter analysis showed severe depletion of all biopterin intermediates.

Deficit of Pterin Synthesis Leading to no production of Serotonin





Identified deficiencies circled in yellow.

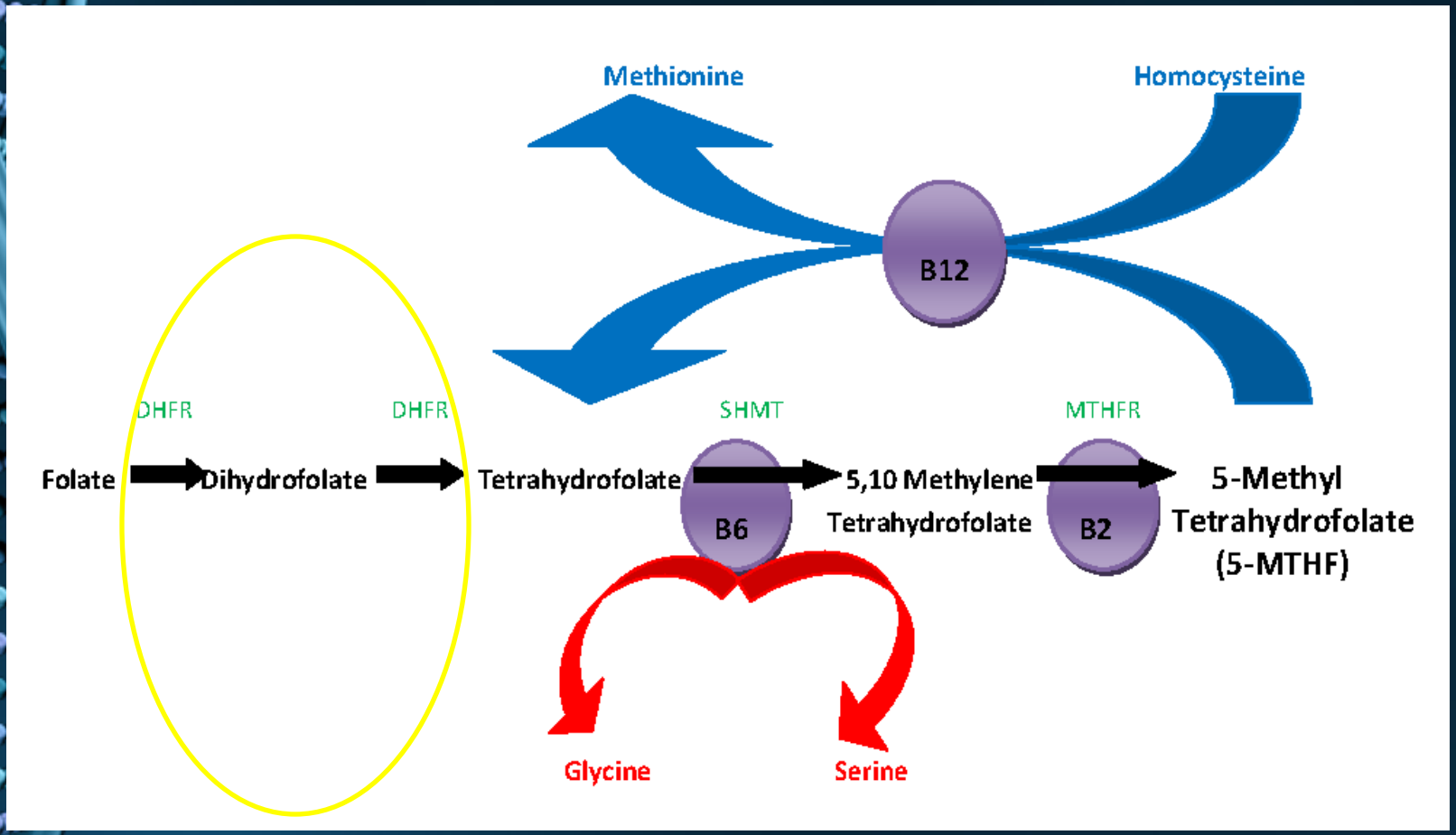
CSF Studies		Range
5HIAA	38	67-140
HVA	116	145-324
Neopterin	<5	7-65
BH4	10	12-30

Treatment with Sapropterin

- The patient reported “better decision making” and “not seeing suicide as an option” in the first four weeks of treatment.
- He also reported odd emotionality including crying about small things, inappropriate feelings of love, and had some mild hypomania.
- Suicidality resolved but mood still low…treated with 5HTP and carbidopa with good response.
- Patient remains stable 5 years later and 3 other patients have responded.

A second patient with treatment refractory depression and suicidal behavior

- Young woman with a significant major depressive disorder and sudden mood fluctuations.
- She had history of non-suicidal self-injury and multiple suicide attempts.
- Her symptoms partially remitted with high dose serotonin reuptake inhibitor and cognitive behavioral therapy.
- Despite partial response, she continued to have sudden dips in mood with significant suicidal ideation and recurrence of non-suicidal self injury.



Folate Metabolism (simplified). DHFR *dihydrofolate reductase* SHMT *serine hydromethyltransferase* MTHFR *methylenetetrahydrofolate reductase*

A second patient (continued)

- CSF testing revealed low 5MTHF level of 35 (normal range 40-120). CSF 5-HIAA, HVA, neopterin, and biopterin were within normal limits.

- Plasma testing revealed normal hemoglobin (13.8), hematocrit (40), serum B12 (937), and folate (14.4) levels.

- In light of her low CSF 5-MTHF, we initiated treatment with Folinic Acid at 5 mg PO daily.

- The patient reported reduction in mood fluctuation, resolution of suicidal ideation, and improvement in mood after 8 weeks. She denied side effects.

- Folinic Acid was increased to 10 mg po daily at 8 weeks. In the following months, patient reported continued stable improvement of mood. Titrated to 1mg/kg.

Cerebral Folate Deficiency

- Cerebral folate deficiency [5-methyltetrahydrofolate (5-MTHF) deficiency] is believed to be caused by inefficient folate transport across the blood brain barrier.

- It is a CNS specific syndrome with low 5-MTHF in CSF and normal folate in plasma because folate is deconjugated and carried across the blood-brain barrier as 5-MTHF.

- Therefore, definitive diagnosis of cerebral folate deficiency requires CSF sampling.

- Low 5-MTHF may also contribute to impaired tetrahydrobiopterin synthesis leading to impairment of serotonin, norepinephrine, and dopamine synthesis.

Folinic Acid

- Folinic acid bypasses deconjugation and reduction steps for folic acid metabolism, i.e. deconjugation to 5-MTHF occurs without dihydrofolate reductase .

- 5-MTHF is then available for transport across the blood brain barrier.

- Folinic acid is a vitamer of folate, with the same activity.

- Dosing may be titrated to 1-2 mg/kg or higher.

Treatment resistant depression

- 15% of depressed patients do not respond to any known therapeutics.
- High rate of disability and mortality due to suicide.
- Metabolomic approaches have not been used to characterize treatment resistant depression.
- We began this investigative path after identifying our first patient; replacement therapy with sapropterin resulted in recovery.
- Therefore, we conducted a case-control study of the prevalence of metabolomic abnormalities in patients with treatment resistant depression.

Recruitment

- Age 14-40 years.
- Failure of at least three full dose and adequate duration medication trials.
- Study requires testing of cerebrospinal fluid, blood, and urine samples.
- N = 50 affected and 18 controls.

Metabolic Disorders with Treatment Refractory Depression

Possible Metabolic Disorder	Cases (N=50)	Controls (N=18)
Cerebral folate deficiency	19	0
Tetrahydrobiopterin deficiency	4	0
Abnormal Acylcarnitine Profile	7	0
Fabry Disease	1	0
? AGAT or GAMT deficiency variant	1	0
No identified disorder	20	18
Total possible Metabolic Disorder	30	0

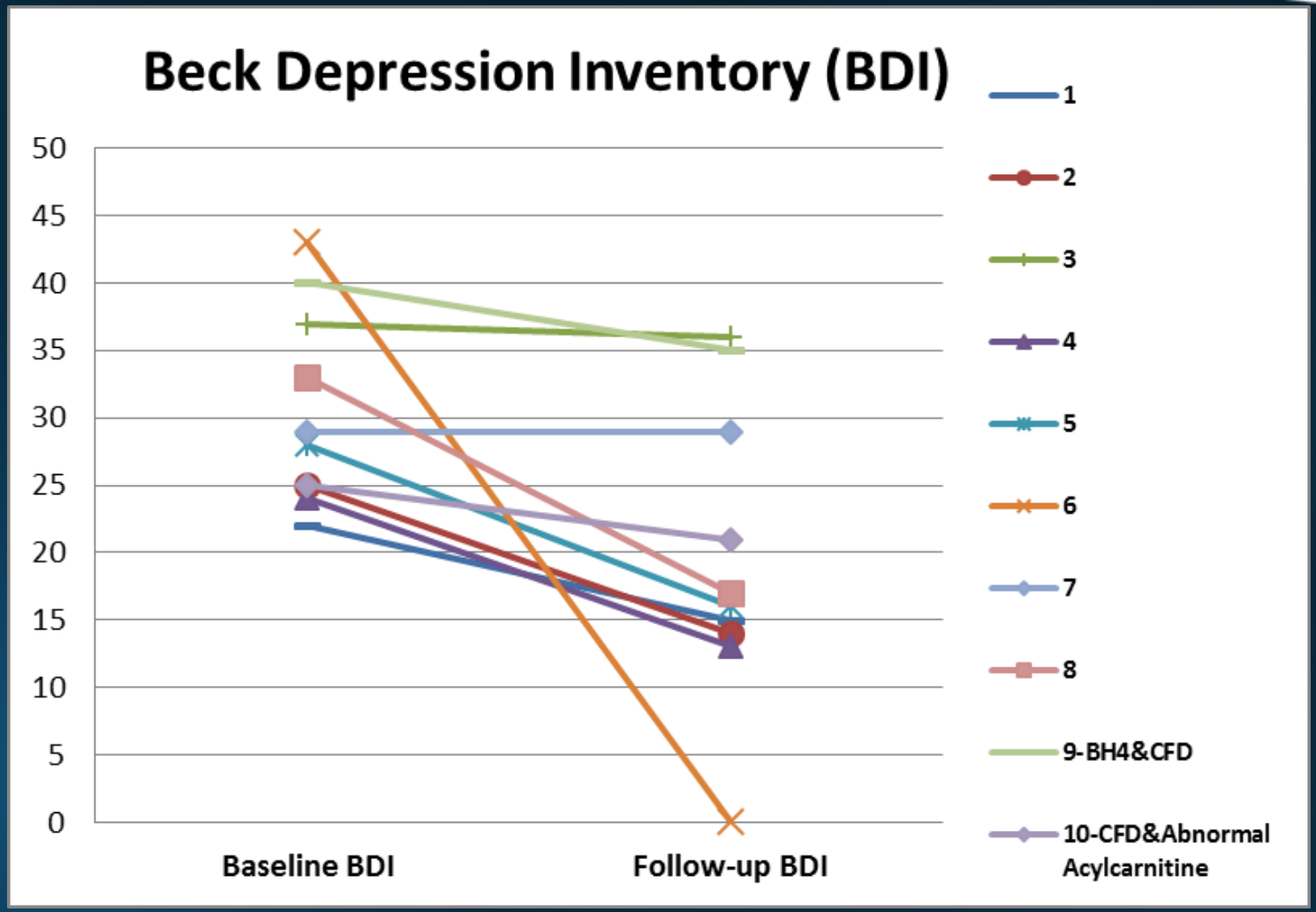
* does not include 4 abnormal microarray findings
* 2 patients had two findings

Metabolic Disorders with Treatment Refractory Depression and Suicide Attempt History

- 60% of affected participants had an identified metabolomic abnormality.
- New treatment available in majority of affected participants recruited so far.
- No healthy controls with an identified abnormality.

Clinical Implications

- **Treatment with folinic acid has resulted in sustained improvement of depressive symptoms in 9 of 10 subjects with adequate treatment time and follow-up.**
- **Evidenced by improvement on the Beck Depression Inventory and the Suicidal Ideation Questionnaire.**
- **New treatments available based on study findings.**



(Baseline BDI 30.6± 7.3>Follow-up BDI 19.6± 11.04; [Z=2.0], p=0.022)

BH4=tetrahydrobiopterin, CFD= cerebral folate deficiency

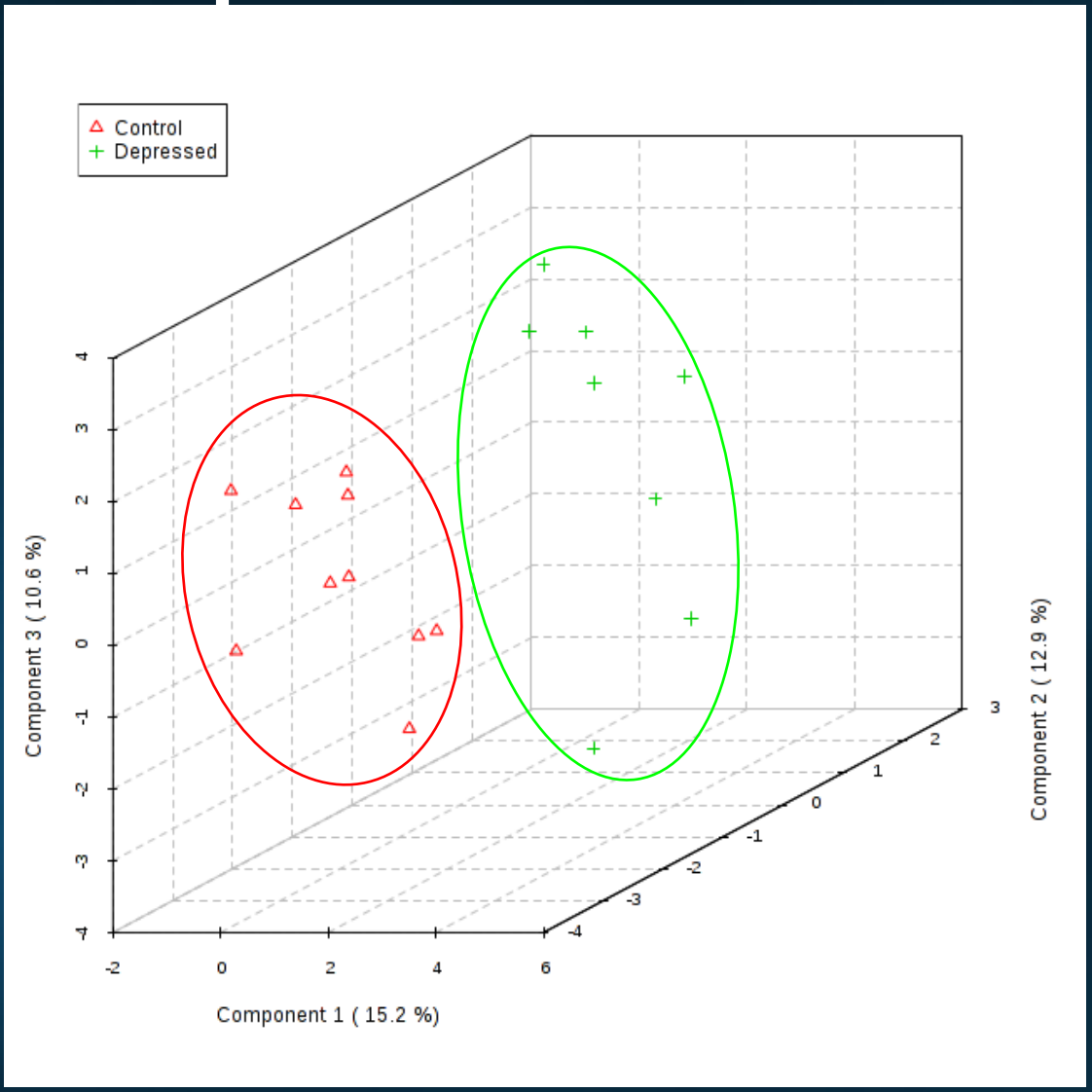
Whole Exome Sequencing

Whole exome sequencing in families of participants with an identified metabolic abnormality.

Identifying variants in common pathways pending.

In one family with cerebral folate deficiency we have confirmed a variant in FOLR1 in which intron 5 is retained.

Broad Spectrum Metabolomics



PLS-DA (3D plot)

Preliminary data

Clear separation in the metabotypes of plasma samples from control and depressed individuals.

Conclusions

- **60% of treatment-resistant depressed patients have metabolomic abnormalities.**
- **The most common disorder was cerebral folate deficiency, characterized by low CSF folate and normal serum folate.**
- **The majority of these patients have shown symptomatic improvement with replacement therapy (e.g. folinic acid, riboflavin, sapropterin).**
- **Metabolic abnormalities may be more common in treatment resistant depressed patients than previously thought, and may suggest novel, effective therapeutic approaches for patients who have been ill for decades.**

Future Directions

- Continue analyzing affected adolescents evaluating blood, urine, CSF for evidence of metabolic disorders.
- Continued analyses of CSF and plasma with broad-spectrum metabolomics.
- Exome sequencing and functional studies.
- Beginning methylomics, markers of cell type in CSF to determine areas of cell damage.

Thank you

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