One carbon metabolic pathway deficiency increases risk for autistic-like behavior in mice.

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HYPOTHESIS

Maternal and child low activity of one carbon metabolism (genetic or environmental) predispose the developing brain to ASD.

Genetic: polymorphism in genes encoding for enzymes of C1 metabolism
Environmental: in-utero environment, lactation, nutrition including food selectivity, GI···
Objectives

Test of hypothesis (mouse)

Regional Autism Database (human)

MTHFR deficiency, Evaluation of outcome and origin. (behavioral and molecular pathways and markers)

Regional Autism Database (obstetrics, gynecology, neonatology, psychiatric, genetic, bio-bank)

Optimization of dietary intervention to Reduce behavioral, molecular and epigenetic outcome. Search for Markers.

Evaluation of risk factors and C1 metabolism involvement (in the database)

Adjustment of diet to genotype, age, sex

Genotype dependent adjustment of supplementation to reduce the risk for ASD and attenuate the symptoms in affected children.
Aim I

To develop personalized intervention for two target populations:

1) Pregnant women with compromised one carbon metabolism to reduce the risk for autism among their newborns.

2) Autistic patients with one carbon metabolism imbalances.
Behavioral Phenotyping

Repetitive behavior

Vocalization in social context

Exploration and anxiety

Object preference

Social interactions - Sociability and social preference

a) S1 b) S1 E c) S1 S2
<table>
<thead>
<tr>
<th>Age \ Sex</th>
<th>Variable</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genotype</td>
<td>Maternal</td>
<td>Offspring</td>
</tr>
<tr>
<td><strong>Neonatal</strong></td>
<td><strong>Weight and morphogenesis</strong></td>
<td>delay</td>
<td>no effect</td>
</tr>
<tr>
<td>P4-P17</td>
<td><strong>Geotaxis</strong></td>
<td>delay</td>
<td>early</td>
</tr>
<tr>
<td><strong>Developmental milestones</strong></td>
<td><strong>Rotarod</strong></td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td></td>
<td><strong>Nest finding</strong></td>
<td>delay</td>
<td>early</td>
</tr>
<tr>
<td></td>
<td><strong>Cliff avoidance</strong></td>
<td>no effect</td>
<td>delay</td>
</tr>
<tr>
<td><strong>Adult - P80</strong></td>
<td><strong>Repetitive behavior (Marble Burying and Nest building)</strong></td>
<td>effect (direction not clear)</td>
<td>repetitive behavior</td>
</tr>
<tr>
<td></td>
<td><strong>Restricted interest (Object preference)</strong></td>
<td>no restricted interest</td>
<td>no effect</td>
</tr>
<tr>
<td></td>
<td><strong>Social - Social preference</strong></td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td></td>
<td><strong>Social - Social novelty preference</strong></td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td><strong>Adult - P80</strong></td>
<td><strong>Aggressive Social interaction – Resident intruder</strong></td>
<td>aggressiveness</td>
<td>aggressiveness</td>
</tr>
<tr>
<td></td>
<td><strong>Recognition memory – Object recognition</strong></td>
<td>no effect</td>
<td>poor performance</td>
</tr>
<tr>
<td></td>
<td><strong>Anxiety – anxiety index</strong></td>
<td>no effect</td>
<td>increased anxiety</td>
</tr>
</tbody>
</table>
Inhibitory neurons in the Prefrontal cortex and cingulate cortex

GAD65-tdTomato
Parvalbumin

Somatostatin
Altered laminar distribution of PV neurons in the cingulate cortex

Sadigurschi and Golan., Genes, Brain and Behavior, 2018
Inhibitory neurons layer acquisition correlate with ASD like phenotype

![Graph A](image)

A) 
- **social**
- **non social**

![Graph B](image)

B) 
- **Normal**
- **Repetitive**

PV cell (cell/mm²)

Cingulate cortex layers

![Images](image)

**NeuN**

GAD-tdTomato

Parvalbumin
Prenatal intervention reduced autistic-like behavior rates.

Cerebral Cortex

Basal Forebrain

Orenbuch et al., under revision, 2019
GABA pathway proteins in the cerebral cortex

Male & Female

Orenbuch et al., under revision, 2019
Aim II:

Find the developmental origin and trajectories

Questions:

Who should we “treat”?

When can we detect first signs of autistic-like behavior?

Which variable in the pups are predictive for later autistic-like behavior in mice?
Characteristics of the pup - mother communication by ultrasonic vocalization calls

Sensory sensitivity:

Light

Sounds

Gravity - geotaxis

Origin of impairment in the GABAergic system (implications for treatment)
Test of hypothesis (mouse)

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National Autism Database (human)

National Autism Database (obstetrics, gynecology, neonatology, psychiatric, genetic, bio-bank)

Evaluation of risk factors and C1 metabolism involvement (in the database)

Genotype dependent adjustment of supplementation to reduce the risk for ASD and attenuate the symptoms in affected children.
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