Title: A mouse model for the study of environmental - genetic interactions leading to Autistic-like behavior.
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Duration of the funding: 3 years

Background: Autism spectrum disorders (ASD) comprise a range of neurodevelopmental syndromes defined by disturbances in three main categories of behavior—social interaction, communication deficits and ritualistic-repetitive behavior—that are usually detected in early childhood. More than 2 folds increase in incidence of autism in recent years suggest a complex genetic and environmental interaction supporting strong link to environmental factors. One of the major time periods during which DNA is responsive to modulation is the very early stages of embryogenesis. During these stages, methylation takes place to stabilize the DNA and control strictly to the developmental plan. Methylation is a gene-specific response and occurs along regions of the DNA that contain certain structures. Polymorphism in the gene Mthfr [methylene tetrahydrofolate reductase] induces global hypomethylation of the DNA, with various genes affected.

Research Hypothesis: A combination of medication with an antiepileptic/neuroleptic drugs and a mutation of the Mthfr gene contributes to low levels of DNA methylation, which may, in turn cause reprogramming of the genome expression and hence a disturbance of brain development. Therefore, changes in DNA methylation are expected to influence a whole network of genes.

Aims: To explore the possibility that Mthfr gene polymorphism and an antiepileptic/neuroleptic drugs will act synergistically to consistently hypomethylate the DNA and thereby influence the expression of gene groups, resulting in autistic behavior.

Methods: The model was validated with behavioral tools for measuring sociability and ritualistic behavior. The expression of candidate genes was examined by real-time PCR and western blot. DNA methylation level were examined by Southern blot.

Results: We found a gender dependent effect of Mthfr genotype and vigabatrin (GVG) neonatal medication on anxiety related behavior and sociability, which correlate gender dependent effect on reelin, FMRP and AMPAR subunits GluR1 and GluR2 in the cortex of the affected mice. In contrast gender independent deficit in recognition memory was in Mthfr deficient and GVG treated mice correlated with gender independent effect on reelin pathway and FMRP levels in the hippocampus. Moreover, in-uterus Mthfr deficient environment was found to interact with neonatal GVG treatment to alter adult mice anxiety in the open field and elevated plus maze and to increase the ratio of AMPAR subunits GluR1/GluR2 in the hippocampus of the affected mice. Finally, several of the effects observed were sensitive to the age of GVG treatment.

Discussion: Mthfr deficient genotype in mice interacts with neonatal GVG to modify anxiety, sociability and memory in adult mice. In addition, part of these effects was gender dependent. The correlation between behavioral impairment and the alteration in reelin and FMRP levels in the relevant brain area support their critical role in the phenotype. Maternal genotype was proven to be a very relevant variable that may aggravates brain susceptibility to environmental factors.

Conclusions: The results of this study support the importance of the Mthfr status in the mother and newborn in the sensitivity of the immature brain to environmental factor and drugs.

Key words: Mthfr, methylation, autism, synapse, social behavior.
Publications associated with the project:


