GRIN1 DNA methylation in peripheral blood of early-onset schizophrenia patients with childhood trauma

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Introduction

- GRIN1 is an essential NMDAR gene¹ and has been identified as a candidate gene in schizophrenia². In addition, evidences suggest that the childhood trauma may affect the DNA methylation patterns, altering the gene and protein expressions in psychiatric disorders³.
- We have tested the hypothesis that the childhood trauma affects the epigenetic factor of DNA methylation in the GRIN1 gene contributing to psychosis and that DNA methylation changes the NR1 protein.

Aims

- To investigate an epigenetic factor, DNA methylation, in one NMDAR subunit gene, GRIN1, in DNA from blood of first episode psychosis patients (FEP), their unaffected siblings and community-based controls with childhood trauma in a Brazilian catchment area.

Methods

Design

- Cross-sectional study of FEP patients (1st April 2012 to 31st March 2015), population-based in Ribeirão Preto, São Paulo State, Brazil⁴.

Inclusion Criteria (STREAM study)	60 FEP	30 Siblings	60 Community-based controls
Residing in Ribeirão Preto catchment area	X	X	X
Age: 16-64 years old	X	X	X
First contact with mental health services due to psychotic symptoms	X		
Psychotic symptoms not related to other medical condition or substance intoxication/withdrawal	X		
No history of psychotic symptoms		X	X
Diagnosis assessment (Structured Clinical Interview for DSM-IV, clinical version, SCID-CV)	X	X	X

Childhood trauma assessment

- Childhood Trauma Questionnaire (CTQ)⁵: 25 Likert-type items that includes five subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect); and we applied the cut-off score as 51 points to classify individuals with or without trauma.
- In addition, we considered a pre-defined⁶ cut-off score based on the moderate to severe threshold (≥ 13 for emotional abuse; ≥ 10 for physical abuse; ≥ 8 for sexual abuse; ≥ 15 for emotional neglect; and ≥ 10 for physical neglect) to classify participants in the maltreated (moderate to severe; severe to extreme) or non-maltreated (none to low; low to moderate) groups, as published previously⁷.

Data analysis

- IBM SPSS, Version 24.0;
- One-way ANOVA and Student's T-test: childhood trauma and GRIN1 methylation;
- Pearson's correlation: GRIN1 methylation and NR1 plasma concentrations.

Results

Figure 1. Increased GRIN1 methylation in individuals with childhood trauma

Figure 2. GRIN1 hypermethylation in FEP patients with emotional neglect

Figure 3. Increased GRIN1 methylation in siblings with physical neglect

Figure 4. Negative correlation between GRIN1 methylation and NR1 plasma concentrations in FEP patients with emotional abuse

⁷ Data already published.

Conclusions

- This is the first study demonstrating the association of GRIN1 DNA methylation in individuals with childhood trauma.
- Our findings suggest that the childhood trauma may concern the GRIN1 methylation, contributing to understand the epigenetics mechanisms by which early life stress affects the glutamatergic system.
- Furthermore, DNA methylation changes of GRIN1 may be associated with NMDAR hypofunction in the pathophysiology of psychosis, considering that NR1 is indispensable for functional NMDAR assemblies.

Financial Support

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¹ Paoletti et al., 2013. Nat. Rev. Neuroscience; ² Liu et al., 2019. BMC Med Genet.; ³ Tomassi and Tosato, 2017. Neurosci. Biobehav. Rev.; ⁴ Del-Ben et al., 2019. Br. J. Psychiatry; ⁵ Grassi-Oliveira et al., 2006. Rev. Saúde Pública; ⁶ Bernstein et al., 2003. Child Abus. Negl.; ⁷ Corsi-Zuelli et al., 2019. Psychological Medicine; ⁸ Loureiro et al., 2018. Schizophrenia Research.