Causal effect of Fibroblast growth factor-2 on Bipolar risk: A Mendelian randomization analysis

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Background

Bipolar disorder (BD) is a severe mental disorder which influences daily life and cognitive function. Several studies aim to explore the potential mechanism or molecular target for the therapeutic purpose. In our pilot study, the fibroblast growth factor-2 (FGF2), which regulates angiogenesis and plays a role in neurogenesis was found to be significantly lower in BD patients (7.0±6.1 vs. 15.8±13.7 pg/mL, p=0.011). However, the causality of FGF2 and BD disease risk remained unknown.

Aims & Objectives

(1) To investigate the causal relationship between plasma FGF2 and BD risk through Mendelian randomization (MR). (2) To investigate the correlation between FGF2 and cognitive performance in BD patients.

Methods

Two-sample MR analysis was conducted to access the putative causal relationships between plasma FGF2 (exposure) and BD (outcome) using genetic variants located in *FGF2* as instrument. Effect size for SNPs to BD risk were obtained from Taiwan Biobank (TWB) cohort using TWB 2.0 array. Plasma FGF2 level was determined by commercial ELISA kit (Quantikine, R&D Systems) from National Cheng Kung university hospital (NCKUH) cohort. Cognitive function was measured by the Wisconsin Card Sorting Test (WCST) and Continuous Performance Test (CPT).

Results

In the TWB cohort, we extracted 580 BD cases and 1740 controls. For the NCKUH cohort, we included 133 BD patients and 58 control with cognitive measurement. Worse cognitive function was noted in BD patients for WCST, and CPT. Plasma FGF2 was lower in BD patients than controls (7.9 ± 7.8 and 13.2 ± 14.7, p= 0.015). For MR, two SNPs showed significant association between plasma FGF2 level and BD risk ($F_{BD/logFGF2}$ =2.29, p< 0.001 for rs118045111, and $F_{BD/logFGF2}$ =2.01, p< 0.001 for Affx-23303065). Furthermore, the plasma FGF2 levels were negatively associated with WCST categories completed in BD patients (*r*= -0.208, *p*= 0.050), unmask CPT in BD patients (*r*= -0.267, *p*= 0.011) and mask CPT in BD patients (*r*= -0.226, *p*= 0.048).

Discussion & Conclusion

From this Mendelian randomization analysis, plasma FGF2 level may be the putative causal factor associated with BD risk, and also be correlated with the cognitive impairment in BD patients. However, the potential mechanism is unclear. More studies are needed to investigate the role of FGF2 in BD illness.