PM495

Neuropathology and functional analysis of schizophrenia associated variant in the MIR137 locus

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Abstract

Small non-coding microRNA (miRNA) coordinate mRNA translation in the brain, and their dysregulation has significant consequences in neurodevelopmental disorders. This hypothesis is supported by strong genetic evidence at the genome-wide associated variant in MIR137 (rs1625579) in recent PGC mega analysis of schizophrenia. We used a TaqMan genotyping and expression strategy to investigate the allelic expression (rs2660304) in post-mortem DLPCF from subjects with schizophrenia and controls with no history of psychiatric disorder (n=74). While no significant difference was observed in the expression of miR-137 in postmortem DLPCF between the controls and schizophrenias, we found that mature miR-137 expression was significantly reduced in the samples homozygous for the risk allele compared to those homozygous for the alternative. Expression in the heterozygotes was not significantly different to either of the homozygotes, however, when we examined the allelic imbalance by differentiating pri-miR-137 expression at each allele (rs2660304), the risk allele was significantly lower compared to the alternative. Functional consequences of dysregulated miR-137 in neurons was then examined human SH-SY5Y neuroblasts electroporated synthetic miR-137 and its antisense antagonist using gene expression profiling. While over expression of miR-137 produced relatively few changes in target gene expression the repression of miR-137 in these cells produced changes in a large number of target genes, many of which have also been associated with schizophrenia. These genes were also enriched in several pathways believed to be involved in the neuropathology of the disorder including, axon guidance, glucocorticoid receptor signalling, ErbB signalling, dopamine-DARPP32 feedback in CAMP signalling, and mTOR signalling. This suggests that the risk variant in MIR137 is an eQTL and results in haploinsufficiency in carriers causing dysfunction in several pathways relevant to schizophrenia.

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How delusion is formed?

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Abstract
Traditionally, delusions have been considered to be the products of misinterpretation and irrationality. However, some theorists have argued that delusions are normal or rational cognitive responses to abnormal experiences. That is, when a recently experienced peculiar event is more plausibly explained by an extraordinary hypothesis, confidence in the veracity of this extraordinary explanation is reinforced. As the number of such experiences, driven by the primary disease process in the perceptual domain, increases, this confidence builds and solidifies, forming a delusion. We tried to understand the formation of delusions using a computer simulation based on Bayesian inference. We found that (1) Even if a delusional explanation is only marginally more plausible than a non-delusional one, the repetition of the same experience results in a firm belief in the delusion. (2) The same process explains the systematization of delusions. (3) If the perceived plausibility of the explanation is not consistent but varies over time, the development of a delusion is delayed.

Additionally, this model may explain why delusions are not corrected by persuasion or rational explanation and why the antipsychotics have limited anti-delusional effect. This Bayesian inference perspective can be a mathematical model of delusions and also considered a way to understand delusions in terms of rational human heuristics. However, such experiences of “rationality” can lead to irrational conclusions, depending on the characteristics of the subject.

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Epigenetic status of LINE-1 promoters in neurons and non-neurons
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Abstract
Human retrotransposon LINE-1 (L1) plays important roles in transcriptional regulation and genome stability. We previously discovered an increase of L1 copy number in the brain tissues of patients with schizophrenia (Bundo et al., Neuron, 2014). To understand the L1 activities in human brains, we investigated distribution of 5-methyl cytosine (5mC) and 5-hydroxymethylcytosine (5hmC) in the L1 promoter regions of human neurons and non-neurons. We separated frontal cortex cells into neuronal and non-neuronal nuclei by NeuN-based nuclei sorting, and performed comprehensive analysis on mC and hmC. We found that full length L1 promoters in neuronal nuclei manifest characteristic mC and hmC pattern in accordance with L1 evolution. Younger L1 subfamilies had less mCs and more possibilities of containing hmCs in their promoters. This pattern was unique to L1 promoters of neuronal nuclei, and independent of the genomic context of L1 insertion. On the other hand, such pattern was not observed in non-neurons or non-full length L1s. Our findings suggest that L1 has distinctive roles in transcriptional regulation in neurons.

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Investigation of feelings toward taking blonanserin and risperidone in schizophrenia patients: part 2
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Abstract
Background: The long-term target of drug therapy for schizophrenia is prevention of recurrence/relapse and rehabilitation into society, for which maintenance of favorable medication adherence is important. We have been investigating the influence of treatment with a base compound of blonanserin (BNS) or risperidone (RIS) on the objective/subjective evaluations of patients.

Methods: Schizophrenic patients treated with RIS as a base compound at the psychiatric outpatient clinic of Kurume University Hospital were allocated to a group with a switch to BNS and RIS dose adjustment, and followed for 24 weeks (randomized open study). The evaluation items were the Drug Attitude Inventory-10 (DAI-10), Life Assessment Scale for the Mentally Ill (LASMI), sexual function, efficacy based on PANSS, and safety based on body weight and prolactin level. Fifteen patients in the BNS group (32.1 ± 6.7 years old) and 15 patients in the RIS group (33.7 ± 7.5 years old) followed for 24 weeks were included in analysis. To evaluate cognitive function, change of oxy-Hb concentration was observed using multi-channel NIRS. Changes in oxy-Hb value were measured at bilateral recording points (22 on each side) while performing a Japanese word chain game (shiritori).

Results: DAI-10 was significantly improved in the BNS group after 20 and 24 weeks compared with that in the RIS group. No significant difference was observed in PANSS. Body weight variation was significantly smaller in the BNS than RIS group at 20 and 24 weeks. The prolactin level was significantly lower in the BNS than RIS group. The oxy-Hb value significantly increased in the frontal pole region only in the BNS group.

Discussion: The feeling toward taking BNS was better than that of RIS, and the incidence of sexual dysfunction was low, suggesting that the medication adherence to BNS is easy to maintain and improves cognitive function.

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Improvement of cognitive function before and after 2-year treatment with long-acting injection (LAI) of antipsychotics evaluated by NIRS using single word-induced hemoglobin variation as an index
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Abstract
Introduction: In drug therapy with long-acting injection (LAI) of antipsychotics, the drug level is maintained by injection every 2-4 weeks, and it is effective for the rehabilitation in schizophrenia patients. In this study, Changes of oxy-Hb concentration...