

Association between LRRTM1 gene DNA methylation and schizophrenia psychopathology

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Age of Onset

- Early adulthood
- Productive years

Employment

- 80% remain unemployed (*Dahlan et al, 2014*)
- Dependent on family

Economic loss

- RM 380 million = 0.04% GDP cost to Nation (*Teoh et al, 2017*)

Signs & Symptoms of Schizophrenia

Positive Symptoms



Dopamine
excess in
mesolimbic
system

**Disorganized
speech and thoughts**

Negative Symptoms



Dopamine
deficit in
mesocortical
system?

Blunted affect

Cognitive Symptoms



Glutamatergic
synaptic
dysregulation
?

**Impaired sensory
perception**

LRRTM1

Leucine rich repeat transmembrane neuronal protein 1

Post-synaptic adhesion molecules

Promotes glutamatergic synapse development (*Siddiqui et al, 2010*)

Deletion leads to loss of hippocampus volume similar to changes in schizophrenia patient (*Takashima et al 2011*)

Deletion disrupts basal synaptic transmission, excitatory synapse function & long term potentiation (*Bhourri et al 2018; Karimi et al 2021*)

DNA METHYLATION

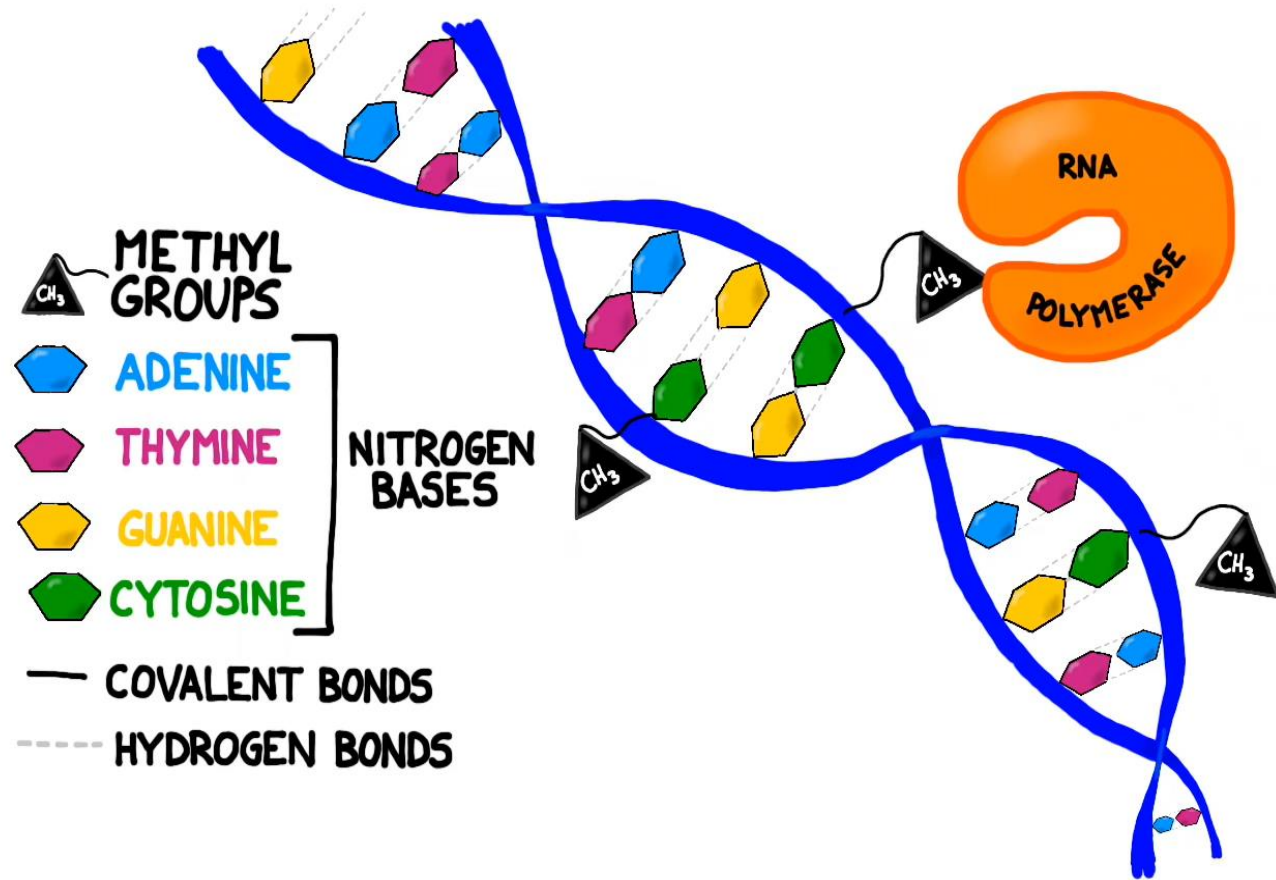
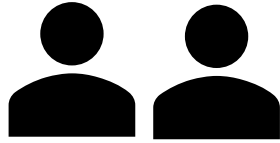
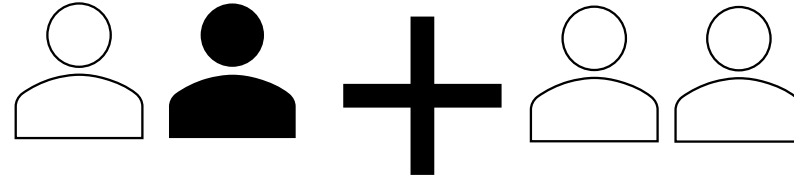


Image credit: BOGOBiology

DNA METHYLATION of LRRTM1 in Schizophrenia



Similar methylation
profile



Less similar
methylation profile



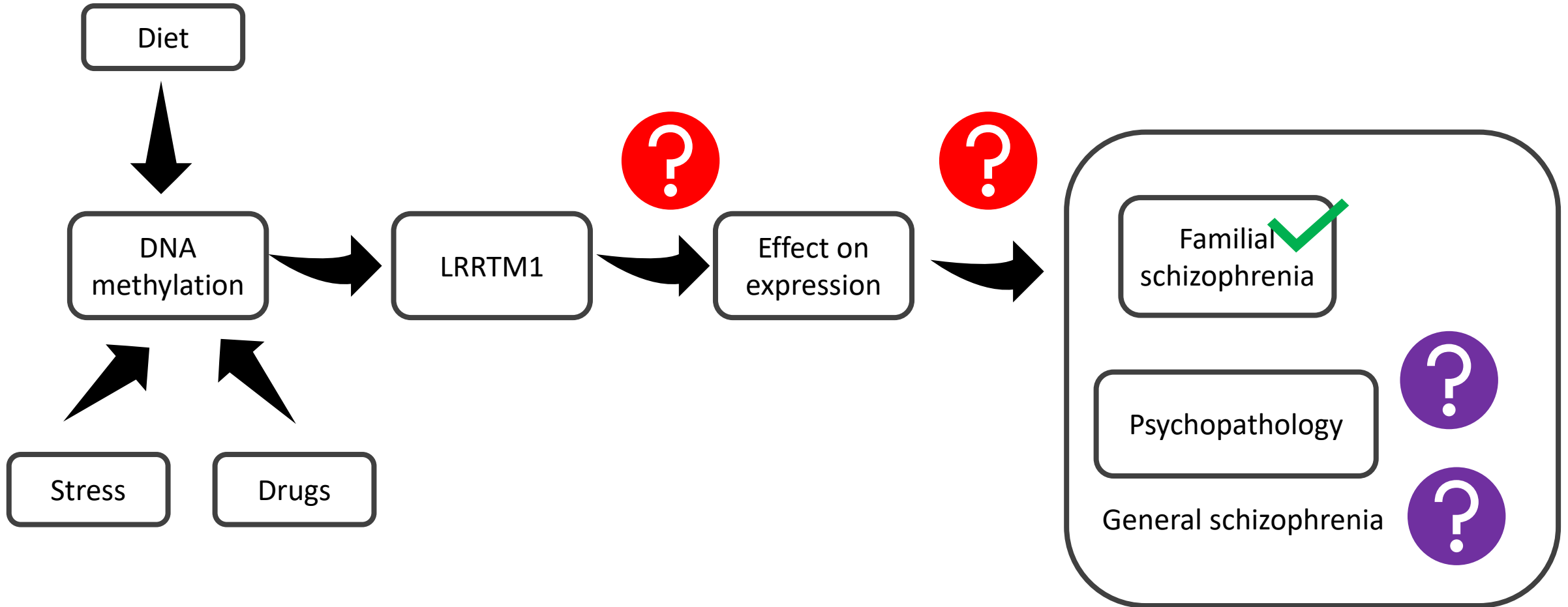
Schizophrenia



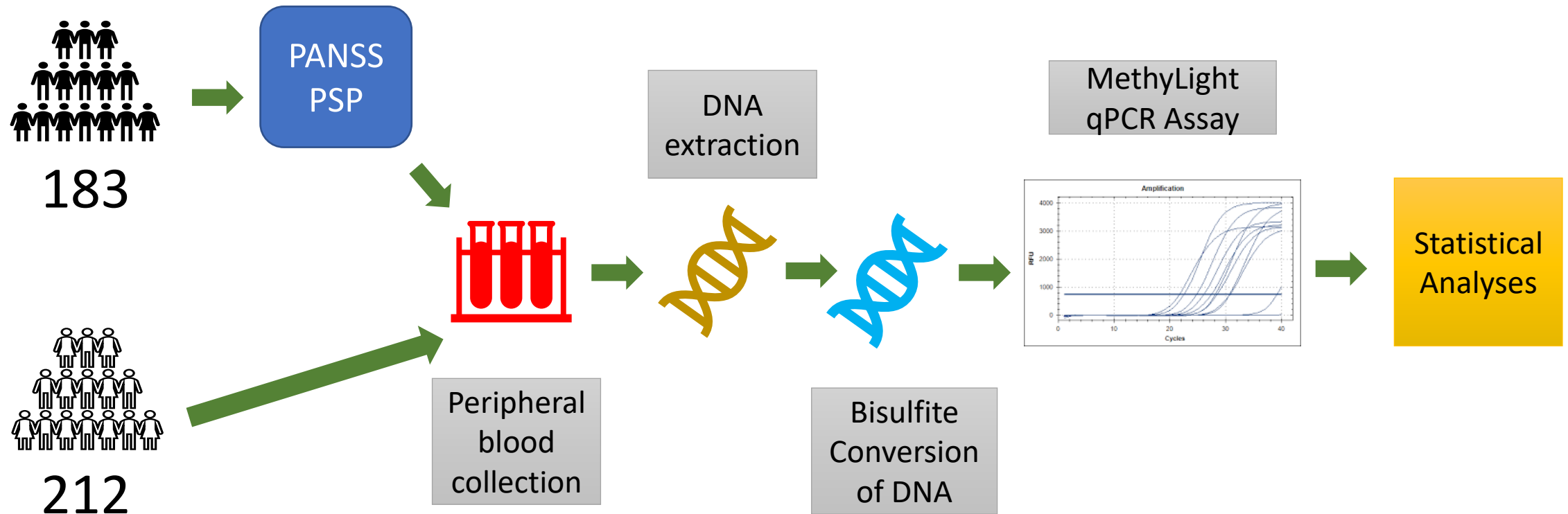
Healthy

(Brucato et al, 2014)

DNA METHYLATION of LRRTM1 in Schizophrenia



METHODOLOGY



PANSS & PSP

Positive and Negative Syndrome Scale (PANSS)	Personal and Social Performance Scale
Clinician administered	Clinician administered
30 items, 3 to 5 domains	4 domains
7 point Likert Scale	6 point Likert Scale
1 (absent) – 7 (extreme)	Absent to Very Severe
Score 30 (absent of symptom) – 210 (most severe symptom)	Score 0 (worst function) – 100 (best function)

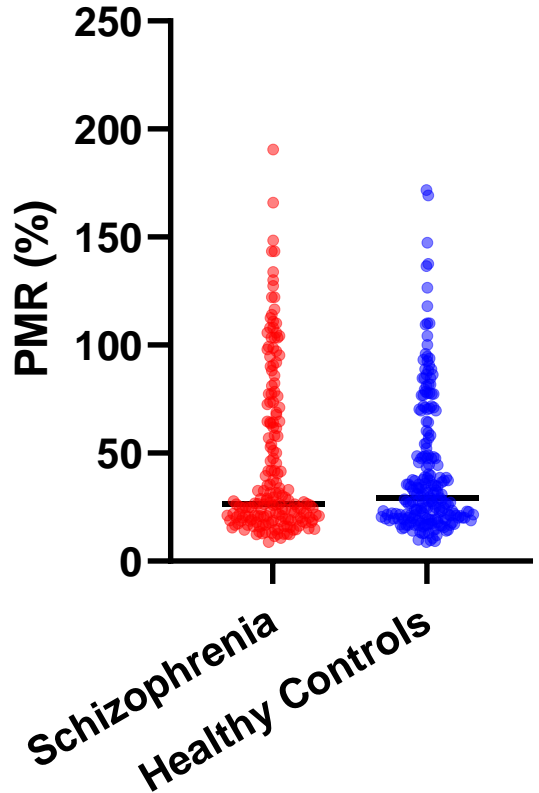
RESULTS - SOCIODEMOGRAPHICS

Table 1 Sociodemographic characteristics of study participants.

Sociodemographic Characteristics	Schizophrenia patients, <i>n</i> = 183	Healthy controls, <i>n</i> = 212	<i>p</i> -value
Age, Years			
median	39.0	38.0	0.309 ¹
(IQR)	(31.0 - 48.0)	(31.0 - 45.0)	
Gender			
Male, % (<i>n</i>)	61.7 (113)	61.3 (130)	0.931 ²
Female, % (<i>n</i>)	38.3 (70)	38.7 (82)	
Ethnicity			
Malay, % (<i>n</i>)	79.2 (145)	72.6 (154)	0.128 ²
Chinese, % (<i>n</i>)	20.8 (38)	27.4 (58)	

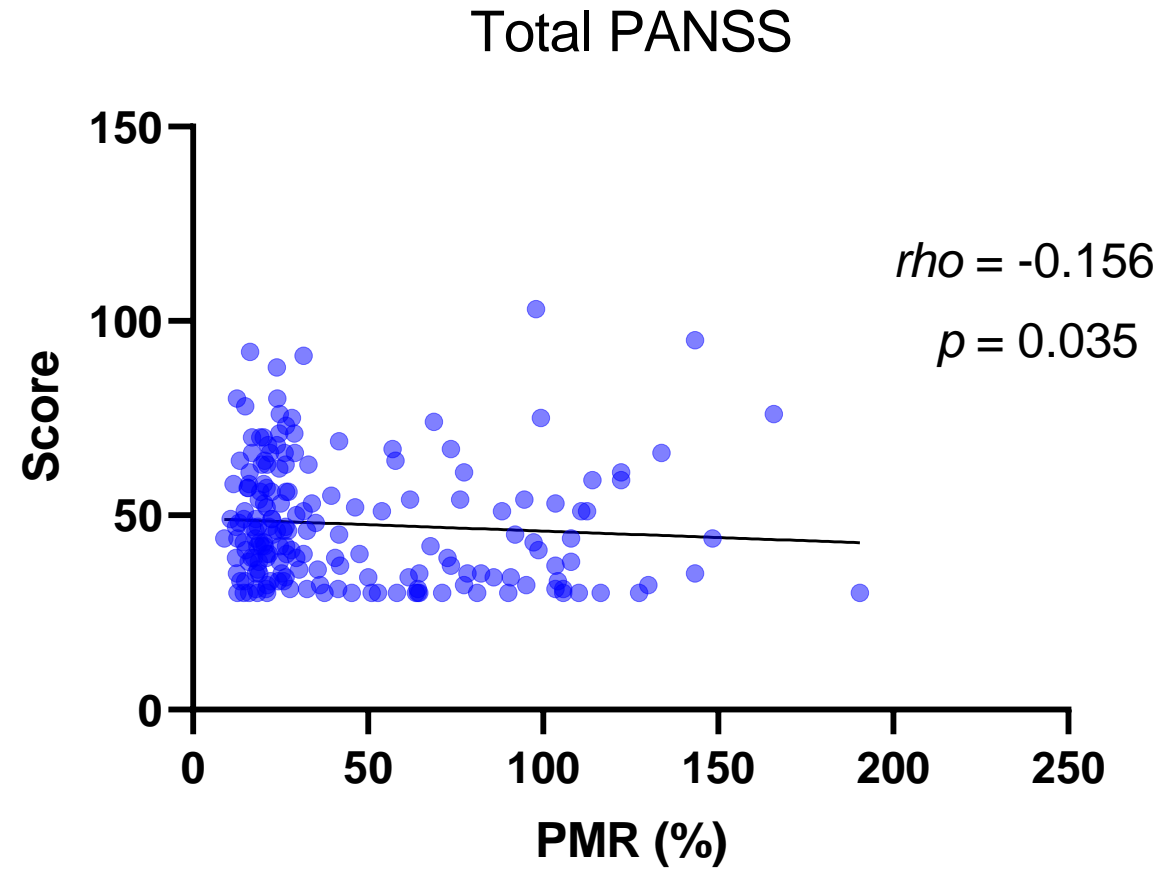
¹Mann-Whitney *U* test; ²Chi-square test; *statistically significant. *n* = number; IQR = interquartile range; BMI = Body Mass Index. *p*-value <0.05 is considered significant at 95% confidence interval.

RESULTS - LRRTM1 DNA METHYLATION IN GROUPS



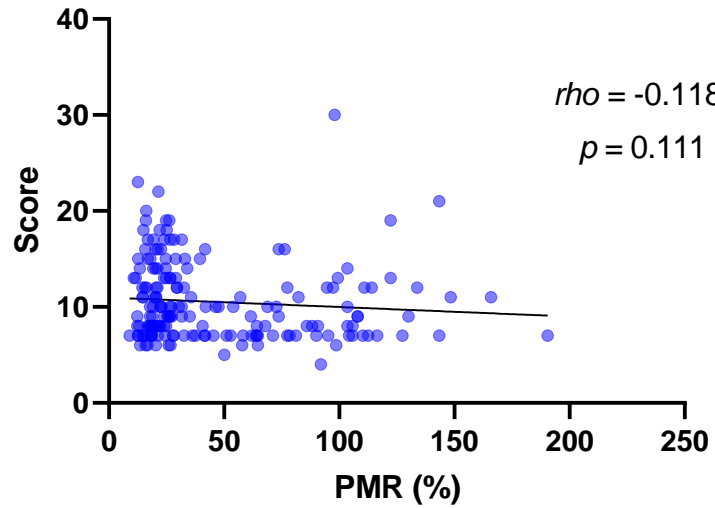
Median PMR Schizophrenia ($n = 183$): 26.61%
Median PMR Healthy Controls ($n = 212$): 29.12%
 $U = 19364, p = 0.976$

RESULTS - PSYCHOPATHOLOGY

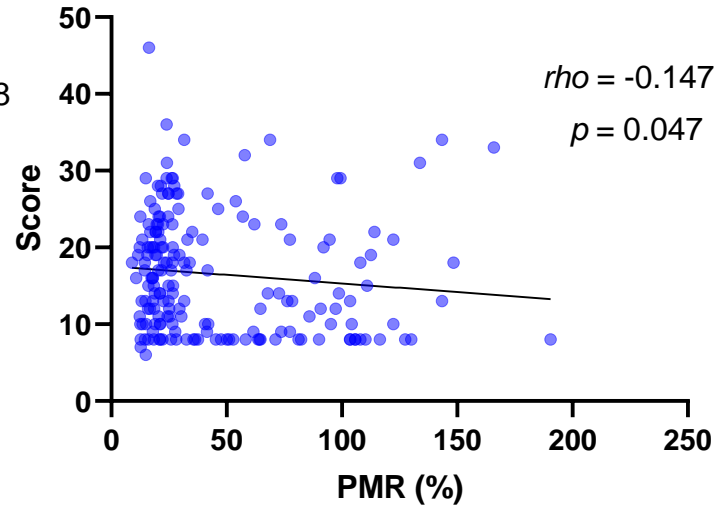


RESULTS - PSYCHOPATHOLOGY

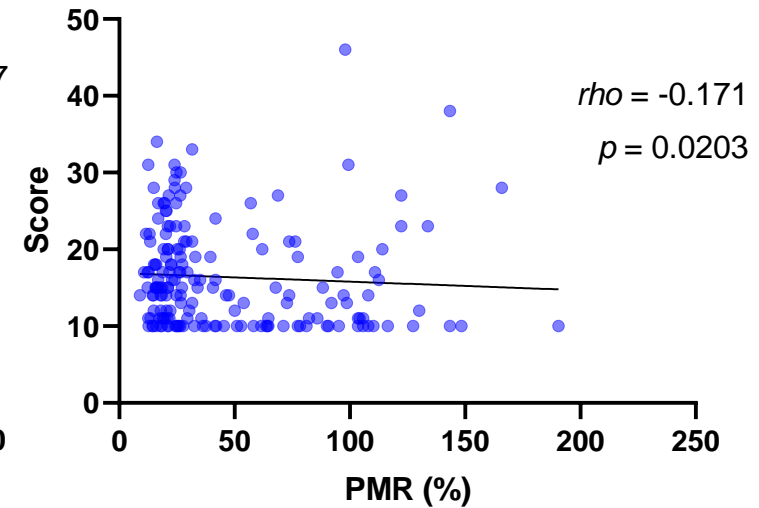
Positive domain



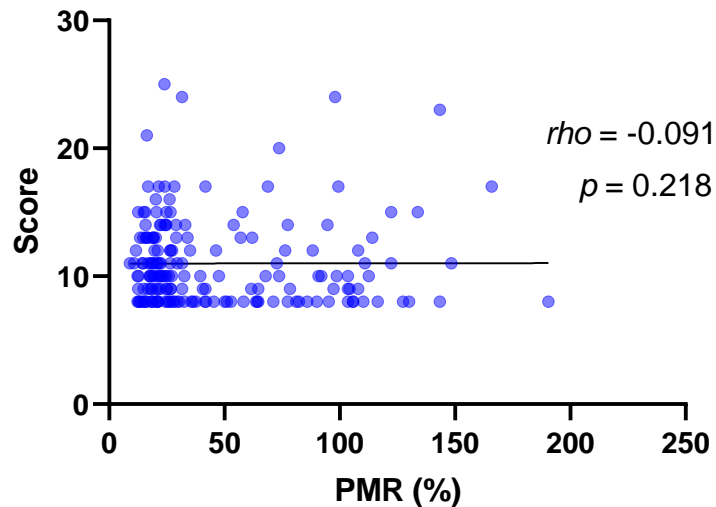
Negative domain



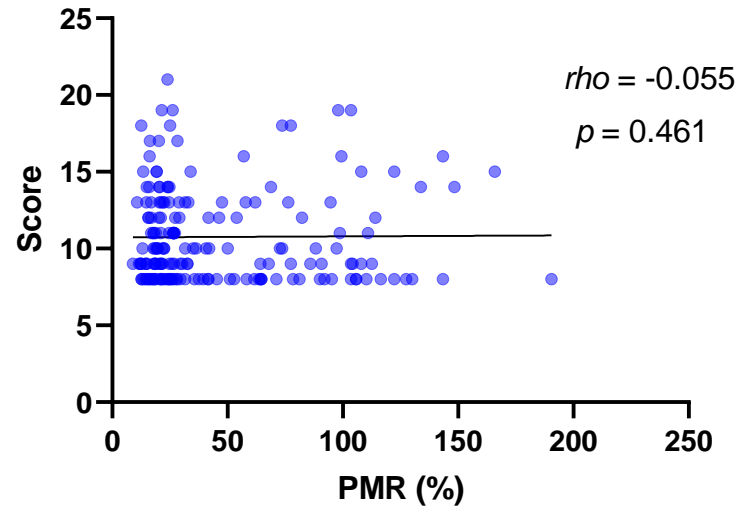
Disorganization domain



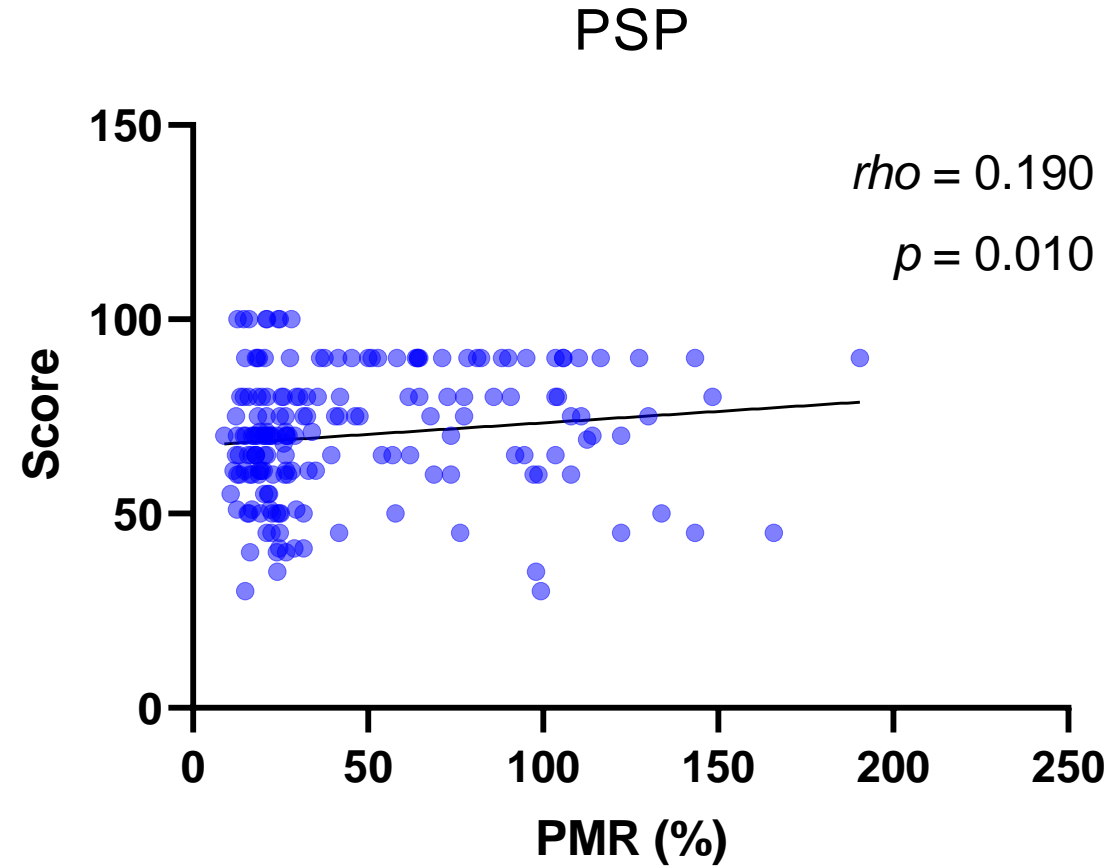
Excitement domain



Depressive domain



RESULTS - PSYCHOPATHOLOGY



DISCUSSION

- ❑ Higher methylation levels of LRRTM1 are linked with better symptoms and functions.
- ❑ This is partly in line with previous study that found higher LRRTM1 methylation levels in healthy people compared to those with familial schizophrenia (*Brucato et al, 2014*).
- ❑ Lack of association between LRRTM1 methylation and general schizophrenia could be due to schizophrenia heterogeneity and complex pathogenesis.

DISCUSSION

- ❑ Using PANSS may help identify the affected phenotypes. In this study, only negative and disorganization symptoms were linked with LRRTM1 methylation.
- ❑ Therefore we suggest segregating patients into phenotypes to better understand the effect of epigenetic modifications in schizophrenia.
- ❑ Since methylation is reversible, further exploration on the mechanism underlying this association could eventually be useful for novel treatment strategy in the future.

LIMITATIONS

- ❑ We did not evaluate the association between DNA methylation and the expression of *LRRTM1*.
- ❑ Other genes related to theory of synapse plasticity were not studied together.
- ❑ Included patients were mostly stable on medication, therefore the methylation levels during active/ relapse phase could not be evaluated.

CONCLUSION

- ❑ DNA methylation of LRRTM1 may be involved in the pathogenesis of subsets of schizophrenia.
- ❑ The cause-effect relationship and the exact mechanism needs to be investigated in future studies.

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