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(please insert ref. above)

The Research Grants Council of Hong Kong
NSFC/RGC Joint Research Scheme
Joint Completion Report

(Please attach a copy of the completion report submitted to the NSFC by the Mainland researcher)

Part A: The Project and Investigator(s)

1. Project Title

Schizophrenia-related de novo and compound heterozygous mutations

2. Investigator(s) and Academic Department/Units Involved

	Hong Kong Team	Mainland Team
Name of Principal Investigator *(with title)*	Prof. Pak Chung SHAM	Prof. Tao Li
Post	Chair Professor	Director
Unit / Department / Institution	Faculty of Medicine The University of Hong Kong	West China Hospital Sichuan University
Contact Information	pcsham@hku.hk	Xuntao26@hotmail.com
Co-investigator(s) *(with title and institution)*	Prof. EYH Chen, HKU Dr. WC Chang, HKU Dr. KW Chan, HKU Dr. HME Lee, HKU Dr. SS Cherny, Tel Aviv U Prof. M Li, Sun Yat-Sen U	Dr. Z Yang, Sichuan U Dr. Q Wang, Sichuan U Dr. B Xiang, Sichuan U Dr. W Deng, Sichuan U Dr. M Li, Sichuan U

3. Project Duration

	Original	Revised	Date of RGC/ Institution Approval *(must be quoted*)
Project Start date	01/01/2015		
Project Completion date	31/12/2018		
Duration *(in month)*	48		
Deadline for Submission of Completion Report	31/12/2019		

Part B: The Completion Report

5. Project Objectives

5.1 Objectives as per original application

1. To identify de novo mutations associated with schizophrenia in the Chinese population
2. To identify compound heterozygous mutations associated with schizophrenia in the Chinese population
3. …

5.2 Revised Objectives

Date of approval from the RGC: _____

Reasons for the change: _____

_____

1.
2.
3. ....

6. Research Outcome

Major findings and research outcome
(maximum 1 page; please make reference to Part C where necessary)

1. Schizophrenia-related de novo variants are enriched in genes involved in prenatal brain development, the frontal, temporal and parietal cortical regions (Wang et al, 2015).
2. Schizophrenia patients have an excess of rare damaging variants in DNA repair and cell cycle pathways; patients with these variants show decreased resting state connectivity between left hippocampus and the cerebellum, and increased resting

state connectivity between left hippocampus and left inferior parietal cortex (Yang et al, 2017)

3. Schizophrenia patients with rare damaging variants in gene sets related to glutamate neurotransmission (NMDA-mediated synaptic currents) are more frequent in non-responders to antipsychotic drugs than in responders (Wang et al, 2018)

Potential for further development of the research and the proposed course of action *(maximum half a page)*

The finding that rare damaging variants in genes related to glutamate neurotransmission are associated with poor response to antipsychotic treatment has the potential to contribute to the development of precision psychiatry. Patients identified to be likely poor responders may require treatments that have alternative targets to current antipsychotic drugs (which are almost exclusively dopamine D2 antagonists.

7. The Layman's Summary

(describe in layman's language the nature, significance and value of the research project, in no more than 200 words)

Schizophrenia is a serious mental disorder characterized by abnormal beliefs and sensory experiences, disordered thinking, and impaired cognitive function. The disorder typically starts in late adolescence or early adulthood, and causes significant decline in educational and occupational performance. Current treatment of schizophrenia is almost exclusive based on drugs that block dopamine D2 receptors, and is effectively in only about 2/3 of patients. The search for effective treatments for treatment-resistant patients is hampered by the difficulties in accessing patients' brains for detailed studies. Genetics offers an alternative approach to finding disease mechanisms. Our project uses modern DNA sequencing technologies to identify genes related to schizophrenia, including those that contribute to the development of the disorders, and those that affect response to current drugs. Our results suggests that genes involved in early brain development may contribute to schizophrenia, and that patients with genetic changes affecting glutamate neurotransmission are more likely to respond poorly to current drugs which act primarily on dopamine. These results suggest new drug targets and indicate that genomic information may help guide treatment for schizophrenia patients.

Part C: Research Output

8. Peer-reviewed journal publication(s) arising directly from this research project

(Please attach a copy of each publication and/or the letter of acceptance if not yet submitted in the previous progress report(s). All listed publications must acknowledge RGC's funding support by quoting the specific grant reference.)

The Latest Status of Publications				Author(s) ***(bold** the authors belonging to the project teams and denote the corresponding author with an asterisk*)*	Title and Journal/ Book *(with the volume, pages and other necessary publishing details specified)*	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*
Year of publication	Year of Acceptance *(For paper accepted but not yet published)*	Under Review	Under Preparation *(optional)*						
2015				**Wang Q**, **Li M, Yang Z**, Hu X, Wu HM, Ni P, Ren H, Deng W, Li M, Ma X, Guo W, Zhao L, Wang Y, Xiang B, Lei W, **Sham PC**, **Li T***	Increased co-expression of genes harboring damaging mutations in Chinese schizophrenic patients during prenatal development. Scientific Reports DOI 10.1038/srep18295	2016	Yes	Yes	No
2016				**Wang Q**, Cheng W, Li M, Ren H, Hu X, Deng W, Ma X, Zhao L, Wang Y, Xiang B, Wu HM, **Sham PC**, Feng J, **Li T***	The CHRM3 gene is implicated in abnormal thalamo-orbital frontal cortex functional connectivity in first-episode treatment-naive patients with schizophrenia. Psychol Med. 46(7):1523-34.	2016	Yes	Yes	No
2017				**Yang Z**, **Li M**, Hu X, **Xiang B**, Deng W, **Wang Q**, Wang Y, Zhao L, Ma X, **Sham, PC**, Northoff G**, Li T***	Rare damaging variants in DNA repair and cell cycle pathways are associated with hippocampal and cognitive dysfunction: a combined genetic imaging study in first-episode treatment-naive patients with schizophrenia. Translational Psychiatry 7, e1028	No	Yes	Yes	No

2018				**Wang Q**, **Wu HM**, Yue W, Yan H, **Zhang Y**, Tan L, **Deng W**, Chen Q, Yang G, Lu T, Wang L, Zhang F, Yang J, Li K, Lv L, Tan Q, Zhang H, Ma X, Yang F, Li L, Wang C, Ma X, Zhao L, Ren H, Yu H, Wang Y, Hu X, Zhang D, **Sham PC***, **Li T***	Effect of Damaging Rare Mutations in Synapse-related Gene-sets on Response to Short-term Antipsychotic Medication in Chinese Patients with Schizophrenia. *JAMA Psychiatry*, 75, 1261-1269	No	Yes	Yes	No
2019				**Zhang Y**, **Li M**, **Wang Q**, **Hsu JS**, **Deng W**, Ma X, Ni P, Zhao L, Tian Y, **Sham PC***, **Li T***	A joint study of whole exome sequencing and structural MRI analysis in major depressive disorder. Psychological Medicine DOI: 10.1017/S0033291719000072	No	Yes	Yes	No
2017				**Li MX***, **Li J**, Li MLJ, Pan ZC, **Hsu JCJ**, Liu DJJ, Zhan XW, Wang JW, Song YQ, **Sham PC***	Robust and rapid algorithms facilitate large-scale whole genome sequencing downstream analysis in an integrative framework. Nucleic Acids Research 45, e75	No	Yes	Yes	No

2018				**Li MX***, **Li J**, **Mak TSH**, Kwan JSH, Xue C, Chen PK, Leung HCM, Cui LQ, **Li T**, **Sham PC***	A powerful conditional gene-based association approach implicated functionally important genes for schizophrenia. Bioinformatics 35, 628-635	No	Yes	Yes	No

Recognized international conference(s) in which paper(s) related to this research project was/were delivered *(Please attach a copy of each delivered paper. All listed papers must acknowledge RGC's funding support by quoting the specific grant reference.)*

Month/Year/ Place	Title	Conference Name	Submitted to RGC *(indicate the year ending of the relevant progress report)*	Attached to this report *(Yes or No)*	Acknowledged the support of this Joint Research Scheme *(Yes or No)*	Accessible from the institutional repository *(Yes or No)*

9. Student(s) trained *(Please attach a copy of the title page of the thesis.)*

Name	Degree registered for	Date of registration	Date of thesis submission/ graduation
Hei Man WU	PhD	2012	2016

10. Other impact *(e.g. award of patents or prizes, collaboration with other research institutions, technology transfer, etc.)*

N.A.