NAME OF PRESENTING AUTHOR: Mohammad Ahangari

EMAIL ADDRESS OF PRESENTING AUTHOR: ahangarim@vcu.edu

Increased Burden of Common Risk Variants Does Not Account for the High Recurrence Risk of Schizophrenia in Multiplex Families

Mohammad Ahangari[1,2], Amanda E Gentry[1], Robert Kirkpatrick[1,3], Brian C Verrelli[4], Tan-Hoang Nguyen[1,3], Kenneth S Kendler[1,3,5], Silviu-Alin Bacanu[1,3,5], Bradley T Webb[6,1], Brien P Riley[1,3,5]

[1] Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA.

[2]Integrative Life Sciences Doctoral Program, Virginia Commonwealth University, Richmond, Virginia, USA.

[3] Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA.

[4] Center for the Study of Biological Complexity, Virginia Commonwealth University, Richmond, Virginia, USA.

[5] Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA.

[6] GenOmics, Bioinformatics, and Translational Research Center, Biostatistics and Epidemiology Division, RTI International, Research Triangle Park, NC, USA.

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ABSTRACT:

Multiplex schizophrenia families show higher recurrence risk compared to the families of singleton cases, but the source of increased familial recurrence risk is unknown. Two possible hypotheses to explain this observation are 1) a higher burden of common risk variants in the families, or 2) segregation of rare high risk variants in the families. We sought to test the first hypothesis in a large, ethnically homogenous sample of multiplex schizophrenia families, singleton cases and controls, all from the population of Ireland. Polygenic risk scores (PRS) based on the 2nd and 3rd Psychiatric Genomics Consortium (PGC) mega-analyses of schizophrenia were constructed for multiplex family members (N=1,005), singleton cases (N = 2,224), and controls (N = 2,284) and analyses were conducted using mixed effects logistic regression which accounts for the family structure as a random effect. The schizophrenia PRS in familial cases did not differ significantly from singleton cases (p=0.82 and p=0.32 for PGC2 and PGC3, respectively). We also show that the unaffected family members have a significantly higher PRS compared to population controls (p<0.001 for PGC2 and PGC3), indicating the presence of a higher burden of common schizophrenia risk variants across family members. These results suggest that a higher burden of common risk variants is unlikely to account for the increased recurrence risk of schizophrenia in multiplex families. In the absence of an elevated PRS in family cases, segregation of rarer variation in the genome, as identified through whole-genome sequencing may explain part of the higher recurrence risk of schizophrenia in multiplex families.

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