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RSEP:ASREMS- revisiting schizophrenia from an evolutionary perspective: an Association study of recent evolutionary markers and Schizophrenia

Upasana Bhattacharyya, Smita N Deshpande, Triptish Bhatia, B.K Thelma

¹University of Delhi South Campus, New Delhi, India

²Department of Psychiatry, PGIMER-Dr. RML Hospital, New Delhi, India

Persistence of schizophrenia in human populations at a high prevalence and with a large heritability estimate despite reduced fertility and increased mortality rate is a Darwinian paradox. Genetic factors predisposing to schizophrenia are claimed to be i) beneficial for the development of important human traits; and ii) are more likely to be located near human accelerated regions (HARs), genomic regions which are extremely conserved across nonhuman species, but have undergone changes since humans diverged from chimpanzees. Majority of HARs function as enhancers, repressors, modifiers, thereby regulating expression of nearby genes. We hypothesize that variants within HARs may disrupt such regulation, thus contributing to disease etiology. Based on functional relevance and prevalence in the South Asian population, 49 HAR single nucleotide polymorphisms (SNPs) were prioritized from the complete repertoire of HARs (n = 2737) and genotyped in a north-Indian schizophrenia case-control cohort. Test of association using two independent cohorts (discovery: n = 930; replication: n = 1104) revealed 3 SNPs (rs3800926, rs3801844, and rs764453) from chromosome 7 and rs77047799 from chromosome 3 to be significantly associated (Bonferroni corrected $P < 0.002-0.000004$). These SNPs alter the expression of neurodevelopmental genes such as *SLC25A13*, *MAD1L1*, and *ULK4*; HOX family genes; and a few genes implicated in mitochondrial function. These SNPs may most likely alter binding sites of transcription factors, including *TFCP2*, *MAFK*, *SREBF2*, *E2F1*, and/or methylation signatures around these genes. These findings reiterate a neurodevelopmental basis of schizophrenia and also open up a promising avenue to investigate HAR-mediated mitochondrial dysfunction in schizophrenia etiology.

Biography

Upasana Bhattacharyya is currently pursuing her PhD at University of Delhi South Campus, New Delhi, India. She has published 4 papers in reputed journals and one book chapter. She has presented her work at multiple reputed international conferences including ASHG, ISHG and IGES. She is a recipient of fellowship from ICMR, CSIR-UGC and training fellowship from NIH.