P-176 - TOO MUCH, BUT ALSO TOO LITTLE OF CALRETICULIN IN THE PSYCHOSIS SPECTRUM

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The majority of single nucleotide polymorphism association studies in psychiatric disorders suffer from lack of reproducibility, necessitating re-sequencing genes for the identification of novel rare variants and deleterious mutations. We have recently reported three low frequency mutations in the proximal promoter of the human calreticulin (CALR) gene at positions -48C, -205T and -220A that co-occur with the spectrum of psychoses, including schizophrenia, schizoaffective disorder, and bipolar disorder type I. The frequency of those mutations was estimated at < 0.0007, and none of those mutations have been detected in the control population ($p < 0.005$). Mutations -48C and -220A were found to increase the expression of the CALR gene. The third mutation at -205T was detected in an isolate case of schizoaffective disorder. In this study, we examined the function of this mutation in the human neuroblastoma BE(2)-C, and non-neural Human Embryonic Kidney-293) cell lines, and show that in contrast with other mutations in the promoter region, which increase expression of the gene, the -205T mutation significantly decreased gene expression in those cell lines in comparison with the wild-type C-nucleotide ($p < 0.0005$, and $p < 0.017$, respectively). We propose that a deviation from normalcy in the level of CALR in either direction is associated with psychosis. We also propose that the psychoses spectrum, at least in part, is a collection of functional mutations that are absent from the control population. Re-sequencing of the candidate gene promoter regions may unravel other mutations linked with psychosis.

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