P-702 - DOWN-TUNING OF THE CALRETICULIN GENE IN THE PROCESS OF HUMAN EVOLUTION

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Tissue-specific expression of the calreticulin (CALR) gene in the brain gray matter in late-adolescence and early adulthood coincides with the expression of the psychoses phenotypes. We report functional mutations at -48, -205 and -220 in the promoter of the human CALR gene that co-occur with the spectrum of psychoses including schizophrenia, schizoaffective disorder, and bipolar disorder type I. None of those mutations have been detected in the control population ($p< 0.005$). Mutation -220 reverts the conserved block harboring nucleotide -220 to the ancestral type. We analyzed the functional implication of this mutation in the human neuroblastoma cell line BE(2)-C, and non-neural Human Embryonic Kidney 293 (HEK-293), and show that the -220A mutation results in a constitutive increase in the expression of the CALR gene ($p< 0.0003$). We checked homology of the first 1000-bp CALR promoter sequence across species, and found that nucleotide -220C is the only human-unique nucleotide in that stretch. The -220A mutation, on the other hand, co-occurs with severe cognition deficit in humans, and is the rule across the species except humans. The -220A mutation is the first reported instance of a cognition-deficit-associated mutation which reverses a human gene promoter to the primitive type. It may be speculated that, at least the basal transcription of the CALR gene, relating to the proximal promoter region, has been decreased during the process of human evolution. We propose that the psychosis spectrum is, at least in part, a collection of functional mutations that are non-existent in the control population.

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