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THE ATF6-CALRETICULIN AXIS: A PRIME MODEL FOR THE CONTRIBUTION OF LOW FREQUENCY DELETERIOUS MUTATIONS TO MAJOR PSYCHIATRIC DISORDERS

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The activating transcription factor 6/calreticulin (ATF6/CALR) axix has a crucial role in the unfolded protein response. We screened the ATF6 and CALR regulatory regions for low frequency mutations linked with major psychiatric disorders. ATF6 and CALR were sequenced in groups of patients (n-780) vs. controls (n=910). Luciferase dual Glo and electromobility shift assay were used to analyze the function of disease-related mutations. We report very low frequency functional mutations in ATF6 and CALR in a spectrum of patients afflicted with major psychiatric disorders and not in the controls. Those mutations had a dominant effect in gene expression and resulted in an increased gene expression vs. the wild-type alleles. We also observed that those mutations significantly alter the effect of the most widely-used mood stabilizer valproic acid (VPA) in human neuronal cell lines LAN-5, U87, and HEK-293, and are indeed the site of action for VPA. Mutation -220A in the promoter of CALR reverses the promoter block to the ancestral type and is the first instance of a cognition-deficit mutation reversing a human gene promoter to the primitive type. We found significant difference in protein binding patterns between mutant -220A and wild-type -220C version. A role for CALR in the evolution of cognition may also be speculated following the characteristics of the -220A mutation. We have, to date, screened 4,034 genes expressed exquisitely in the brain, and conclude that CALR nucleotide -220 is a unique candidate, human-specificity of which may be crucial to higher order brain functions.

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