Human functional studies of ANK3 and CACNA1C from the Greek LOGOS cohort

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The rs10994336 ANK3 and rs1006737 CACNA1C genetic variants have been recently identified as the most consistent, genome-wide significant risk factors for bipolar disorder, while the CACNA1C variant has also been associated with schizophrenia and major depression. We examined the phenotypic consequences of the risk CACNA1C and ANK3 alleles in a large homogeneous cohort of healthy young males (n=543; mean age 22.1±3) recruited from the first wave of the LOGOS project (Learning On Genetics Of Schizophrenia) in Heraklion, Crete. Subjects were tested for sensorimotor gating as assessed by prepulse inhibition (PPI), memory and executive function, startle reactivity and temperament and personality traits. UNPHASED analysis revealed that the CACNA1C risk allele (rs1006737_A) was associated with lower extraversion and higher harm avoidance, trait anxiety and paranoid ideation consistent with a non-specific proneness to anxiety and paranoia; the ANK3 risk allele (rs10994336_T) was associated with lower novelty seeking and behavioral activation scores, consistent with proneness to anhedonia. Both risk alleles were associated with high startle reactivity. A subsample of 270 subjects underwent testing for affective startle modulation using the IAPS (International Affective Picture System). Subjects homozygous for the risk CACNA1C allele presented with enhanced startle modulation especially for the aversive pictures. The results from startle and the affective personality traits are in keeping with other reports and suggest a role of these polymorphisms in threat/stress signal processing, probably in the hippocampus and/or amygdala. None of the risk genotypes affected sensorimotor gating or behavioral performance in an extensive battery of executive function tests in this cohort of healthy males.