Get to know a gene: CACNA1C

Summary: Minimal evidence exists linking CACNA1C as a pharmacogenomic marker, and CACNA1C shows little clinical utility as a disease marker. While there is an association between CACNA1C and bipolar disorder and schizophrenia, the absolute contribution of CACNA1C to disease risk is very small. Therefore, genetic testing for CACNA1C is not recommended at this time.

What is CACNA1C?

CACNA1C encodes the α-1C subunit of the voltage-gated L-type Ca^{2+} channel, which plays a critical role in neurotransmission, gene expression, synaptic plasticity, and memory processes in the brain.[1-7] While CACNA1C has been studied as a potential disease marker for schizophrenia (SCZ), bipolar disorder (BPD), and major depressive disorder (MDD), concrete evidence is lacking to associate genetic variation in CACNA1C with psychiatric medication response.

Is CACNA1C a risk factor for bipolar disorder, schizophrenia, and major depressive disorder?

Single nucleotide polymorphisms (SNPs) within CACNA1C repeatedly reached genome-wide significance ($p<5 \times 10^{-8}$) for an association with SCZ or BPD.[8-14] However, the effect size is small (OR = 1.07-1.18), and CACNA1C is only one of many susceptibility genes that impact the risk for these disorders. Some of the other genes associated with SCZ and BPD include ANK3, TRANK1, ODZ4, and MHC.[13, 15, 16] Additionally, CACNA1C has been linked to MDD, but these results are less consistent.[17]

What do the data say about CACNA1C variation and psychiatric treatment response?

There are currently only four studies that have evaluated the effect of CACNA1C variants on response to psychiatric medications. One study found two SNPs (rs1006737 and rs10848635) were associated with an increased risk of suicidality and worsening of concentration among Caucasians taking citalopram. However, there was no association between CACNA1C genotype and treatment response or rates of remission.[18] A second study that evaluated response to antidepressants found that the risk allele of rs1006737 was associated with better treatment response and rate of remission in one European group (n = 357), but the same allele was associated with an increased rate of treatment-resistant depression in a second European group (n = 218). No associations were found in a third group of Italian ancestry (n = 96).[19] In another study that evaluated response to olanzapine in a Korean population (n = 502), five novel SNPs were associated with improvement of SCZ symptoms in the Positive and Negative Syndrome Scale (PANSS) subscales. However, rs1006737 was found to have no association with treatment and total PANSS score improvements.[20] Lastly, in a Han Chinese population, another polymorphism in CACNA1C (rs2239063) was associated with better treatment response in SCZ patients treated with olanzapine for 6 weeks (n = 884). There were no associations with treatment response and other antipsychotics (n = 2,908).[21]

What is the clinical significance of CACNA1C genotyping?

The actual level of risk conferred by CACNA1C variants is very small. For example, a recent meta-analysis in SCZ determined the odds ratio for a common SNP (rs1006737) to be 1.20 in an Asian population.[22] Based on this data, a pooled relative risk was calculated to be 1.10. Therefore, given a lifetime prevalence of SCZ being ~0.60% [23-26], carriers would be expected to have a 0.64% risk of lifetime SCZ diagnosis, compared to a 0.58% risk for non-carriers.[27] In effect, the CACNA1C variant confers a 0.06% absolute increase in the risk of developing SCZ. Thus, while the diagnostic association appears to be consistent, the absolute contribution of CACNA1C to disease risk is very small, and CACNA1C is only one of many susceptibility genes. Without a proper understanding of the modest clinical impact of CACNA1C variation, testing for CACNA1C may lead to overestimation of disease risk, unnecessary use of psychotropic medications, and undue patient anxiety regarding the development of serious conditions. Furthermore, the limited studies investigating the effect of CACNA1C variants on psychiatric treatment response have not produced any consistent findings. Additional well-designed, independently replicated pharmacogenomic studies are needed to verify whether CACNA1C variation predicts response to psychiatric medications. While CACNA1C remains an intriguing research target, genetic testing for CACNA1C is not recommended at this time.

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