



HOT TOPICS



Brain-enriched CACNA1C isoforms as novel, selective targets for psychiatric indications

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Multiple lines of evidence suggest the Ca_v1.2 voltage-gated calcium channel (VGCC), encoded by *CACNA1C*, as a novel therapeutic target for psychiatric disorders. *CACNA1C* shows robust transdiagnostic associations with psychiatric disorders [1]. Ca_v1.2 is 'druggable' via the existing calcium channel blockers that are prescribed for cardiovascular indications but show evidence of psychiatric benefit [1]. It has a well-described biology and plays a role in neurobiological processes relevant to psychiatric disorders, including synaptic plasticity, and learning and memory [1].

There is a need to identify more selective Ca_v1.2 targets; repurposing the existing calcium channel blockers is unlikely to be feasible due to their cardiovascular effects, which represent side effects in the context of psychiatric conditions. *CACNA1C* encodes a family of Ca_v1.2 isoforms via alternative splicing mechanisms that differ between tissues to produce functionally-distinct Ca_v1.2 channels that vary in many parameters, including biophysical properties [2] and sensitivity to existing calcium channel blockers [3], highlighting that whilst challenging it may be feasible to develop isoform-selective compounds. Thus, brain-enriched isoforms of *CACNA1C*/Ca_v1.2 may represent selective therapeutic targets for psychiatry. However, the identification of such targets was hampered by two key limitations: firstly, most information about *CACNA1C* isoform diversity was obtained in rodents and splicing patterns can differ markedly between species [4]; secondly, because annotated transcripts are typically reconstructed computationally from short-read sequencing data, little was known about the full-length architecture of *CACNA1C* isoforms in any species. Therefore, we developed a novel technical approach to characterise full length isoforms and obtained the isoform profile of *CACNA1C* in human brain [5]. We identified 241 novel *CACNA1C* isoforms, although most were expressed at low levels [5]. However, we obtained our data using bulk tissue, so isoforms expressed at low levels in the pool could be abundant in specific cellular subpopulations. We are now using this method to profile the isoform repertoire of the human cardiovascular system. We believe it likely that the expressed isoforms will be regulated according to tissue type, consistent with existing data [2, 4]. Isoforms that are enriched in the brain, and with little to no expression in the cardiovascular system, provide a starting point for the development of brain-selective compounds.

Our findings highlight how incomplete our understanding of the transcriptome remains. This information is crucial, since

studies that consider gene expression only at the gene level can miss important switches occurring at the level of individual isoforms. The single nucleotide polymorphisms associated with psychiatric illness within *CACNA1C* are non-coding, so may act via effects on isoform expression [1]. Understanding the full-length isoform context is also needed to elucidate the interactive effects of splicing variation on protein function, as splicing events that are distant in genomic space may be in close proximity in the mature protein. Notably, the poor understanding of isoform diversity also pertains to model systems, e.g. rodents and stem cell models. Given profound changes in isoform profiles between species and across development [4, 6], it is important to characterise isoform profiles in these systems to ensure relevance for pathophysiological studies and drug development.

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