Brain-enriched calcium channels in the pathogenesis and treatment of bipolar disorder

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The last few years have seen substantial progress in our understanding of the genetic basis of psychiatric illnesses such as schizophrenia and bipolar disorder. This research will begin to examine how we can move from genetic insights to new therapies by focussing on arguably the most promising set of molecules arising from the recent genetic studies: the voltage gated calcium channels (VGCCs).

Calcium is an important signalling molecule and plays a key role in brain function. There is long-standing evidence that patients with bipolar disorder have abnormalities in calcium function. Recent genetic studies suggest that these abnormalities may be caused, in part, by alterations in the function of the VGCCs. These channels make attractive drug targets for treating bipolar disorder and other psychiatric disorders in which these channels are implicated. However, many different types of VGCCs are produced from a limited number of VGCC genes, and there is a lack of information about the precise types of VGCCs that are present in human brain, and how these channels are changed in psychiatric disorders and in those at higher genetic risk for these illnesses. Neither do we know how the critical brain VGCCs differ from those found elsewhere in the body.

This project will identify the VGCCs present and enriched in human post-mortem brain tissue, compared to other body tissues, and will investigate how they are changed in association with genetic risk for psychiatric disorders, and in the diseases themselves. Once the brain-enriched isoforms are known, we will investigate their function in cell culture systems (including in induced pluripotent stem cells). The specifics of the project will be tailored to the student's skills and interests, but they may investigate these questions using bioinformatics and/or molecular and cellular biology experiments. Crucially, both our analyses and initial experiments will use human brain tissue. This is essential, because the number of different molecules that a single gene produces is much higher in humans than in others species, particularly in human brain, compared with other types of body tissue.

This research will help us to understand the key brain-enriched types of VGCC to target to improve the treatment of psychiatric illnesses, as well as investigating how genetic variation in the VGCCs increases risk for developing them. More broadly, they will also provide a test of how we can begin to move from genetic findings to new treatments.

A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. Cipriani A, Saunders K, Attenburrow MJ, Stefaniak J, Panchal P, Stockton S, Lane TA, Tunbridge EM, Geddes JR, Harrison PJ. Mol Psychiatry. 2016 Oct;21(10):1324-32. doi: 10.1038/mp.2016.86. Epub 2016 May 31.