Title

Non-coding variants in *VAMP2* and *SNAP25* affect gene expression: potential implications in migraine susceptibility

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Abstract

Migraine is a common and complex neurological disease potentially caused by a polygenic interaction of multiple gene variants. Many genes associated with migraine are involved in pathways controlling the synaptic function and neurotransmitters release. However, the molecular mechanisms underpinning migraine need to be further explored.

Recent studies raised the possibility that migraine may arise from the effect of regulatory non-coding variants. In this study, we explored the effect of candidate non-coding variants potentially associated with migraine and predicted to lie within regulatory elements: *VAMP2*_rs1150, *SNAP25*_rs2327264, and *STX1A*_rs6951030. The involvement of these genes, which are constituents of the SNARE complex, in both membrane fusion and neurotransmitter release underscores their significance in migraine pathogenesis. Our reporter gene assays confirmed the impact of at least two of these non-coding variants. *VAMP2* and *SNAP25* risk alleles were associated with a decrease and increase in gene expression, respectively, while *STX1A* risk allele showed a tendency to reduce luciferase activity in neuronal-like cells. Therefore, the *VAMP2*_rs1150 and *SNAP25*_rs2327264 non-coding variants affect gene expression, which may have implications in migraine susceptibility. Based on previous *in silico* analysis, it is plausible that these variants influence the binding of regulators, such as transcription factors and micro-RNAs. Still, further studies exploring these mechanisms would be important to shed light on the association between SNAREs dysregulation and migraine susceptibility.

Keywords

Migraine; Reporter gene assays; SNARE complex; Non-coding variants; *VAMP2*; *SNAP25*; *STX1A*; Gene expression