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Epigenetic modulators of migraine: lncRNAs as possible new therapeutic targets

Tainah Dorado de Oliveira[1], Luana Carvalho dos Santos[1], Renan Cassiano Ratis[2], Elcio Juliatto Piovesan[1], Angelica Beate Winter Boldt[1]

[1]Federal University of Paraná, Curitiba, Brazil
[2]Laboratory of Neurosciences and Behavior, Department of phamacy, UNICENTRO, Paraná, Brazil

Long non-coding RNAs (lncRNA) are major epigenetic regulators of genome expression. They interfere in the development of multiple pathologies, including migraine, which affects 14% of the world's population. This systematic review started in June 2024, following the PRISMA protocol with registration in PROSPERO (CRD42024559621) of the following questions: "Which lncRNAs are involved in the development of migraine? What is their role in the disease?" and using the descriptors "lncRNA" and "migraine" in EMBASE, Scopus, Web of Science and Pubmed. After removing duplicates with the Rayan QRCL platform, 38 out of 66 articles remained. After reading the titles, abstracts and full text, three articles were included. We found eight lncRNAs differentially expressed in migraine: PVT1, MEG3, LINC-ROR, SPRY4-IT1, ADINR, DICER1-AS1, NKILA, uc.48+. The first four act on neuropathic pain pathways in nervous tissue, while the next three interact with NF-κB (increased NF-κB activity probably induces migraine attacks). The last one up-regulates CGPR (a peptide involved in inflammatory pathways that act on migraine, probably through purinergic activation). Patients having migraine with aura present overexpression of PVT1, MEG3, LINC-ROR, and DICER1-AS1, whereas those having migraine without aura overexpress SPRY4-IT and ADINR. Furthermore, migraine patients without aura have lower DICER1-AS1 expression than controls. In addition, we identified eight articles in the Genome-wide Association Studies catalog, reporting associations between headache and genetic variants in 18 other lncRNAs. Among these, five were associated with migraine (LINC01752, ASTN2-AS1, LINC01985, ADAMTSL4-AS2 and UFL1-AS1), but none was mentioned in the articles of the systematic review. They are indeed poorly known, and their roles are best inferred by the neighboring genes whose transcription they probably regulate. The Astrotactin gene (ASTN2-AS1-regulated), presents variants associated with migraine in both European and Asian populations. UFM1-specific ligase 1, regulated by UFL1-AS1, is also associated with migraine both in transcriptomic and proteomic studies. In conclusion, we propose a set of lncRNAs that are possibly involved in regulating the production of migraine-associated genes, as potential targets for therapeutic intervention, also suggesting their inclusion in new experimental designs to elucidate their possible pathophysiological mechanisms in migraine.