Competing targets of microRNA-608 affect anxiety and hypertension.

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Abstract:
MicroRNAs (miRNAs) can repress multiple targets, but how a single de-balanced interaction affects others remained unclear. We found that changing a single miRNA-target interaction can simultaneously affect multiple other miRNA-target interactions and modify physiological phenotype. We show that miR-608 targets acetylcholinesterase (AChE) and demonstrate weakened miR-608 interaction with the rs17228616 AChE allele having a single-nucleotide polymorphism (SNP) in the 3'-untranslated region (3'UTR). In cultured cells, this weakened interaction potentiated miR-608-mediated suppression of other targets, including CDC42 and interleukin-6 (IL6). Postmortem human cortices homozygote for the minor rs17228616 allele showed AChE elevation and CDC42/IL6 decreases compared with major allele homozygotes. Additionally, minor allele heterozygote and homozygote subjects showed reduced cortisol and elevated blood pressure, predicting risk of anxiety and hypertension. Parallel suppression of the conserved brain CDC42 activity by intracerebroventricular ML141 injection caused acute anxiety in mice. We demonstrate that SNPs in miRNA-binding regions could cause expanded downstream effects changing important biological pathways.

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