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Primate-specific microRNA evolved from non-canonical target recognition expands cortical interneuron reportoire

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MicroRNAs (miRNAs) determine cellular functions by regulating target mRNAs through matches to seed regions (positions 2-8), allowing minor deviation in base pairing. Such non-canonical interactions could evolutionally expand miRNA functionality but remain elusive. Here we found that a primate-specific miRNA, which canonically recognizes G-bulge site (positions 5–6) of conserved neuronal miR-124, promotes expansion of neocortical interneuron repertoire. Utilizing single-cell RNA sequencing of the neocortex in transgenic mice expressing this primate-specific miRNA under the nestin promoter, we observed a significant increase in interneurons. Characterization of these interneurons using canonical markers revealed a rise in MEIS2+/LAMP5+ interneurons, which were found to migrate from layer IV to layer I of the neocortex via the medial migratory stream rather than the rostral migratory stream. Furthermore, employing human-specific markers for Lamp5 interneurons, such as NPY, IQGAP2, and NTNG1, we demonstrated that the expanded population in transgenic mice is more similar to primate Lamp5 interneurons than to those in mice. Cross-species analysis using LIGER confirmed that the gene expression patterns of these interneurons closely resemble those of primates. These findings implicate significance of non-canonical miRNA targets as evolutional intermediates, converging to emergent species-specific miRNAs to innovate cellular diversity.