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A long range distal enhancer controls temporal fine-tuning of *PAX6* expression in neuronal precursors

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ABSTRACT

Proper embryonic development relies on a tight control of spatial and temporal gene expression profiles in a highly regulated manner. One good example is the ON/OFF switching of the transcription factor PAX6 that governs important steps of neurogenesis. In the neural tube *PAX6* expression is initiated in neural progenitors through the positive action of retinoic acid signaling and downregulated in neuronal precursors by the bHLH transcription factor NEUROG2. How these two regulatory inputs are integrated at the molecular level to properly fine tune temporal *PAX6* expression is not known. In this study we identified and characterized a 940-bp long distal *cis*-regulatory module (CRM), located far away from the *PAX6* transcription unit and which conveys positive input from RA signaling pathway and indirect repressive signal(s) from NEUROG2. These opposing regulatory signals are integrated through HOMZ, a 94 bp core region within E940 which is evolutionarily conserved in distant organisms such as the zebrafish. We show that within HOMZ, NEUROG2 and RA exert their opposite temporal activities through a short 60 bp region containing a functional RA-responsive element (RARE). We propose a model in which retinoic acid receptors