

## A long-range enhancer at -52 kb drives expression of the COUP-TFII transcription factor in erythroid cells

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### Abstract:

COUP-TFII, encoded by the *NR2F2* gene, is an orphan nuclear receptor highly expressed during embryonic development in several tissues. In erythropoiesis, COUP-TFII is active in yolk sac-derived cells prior to the switch to adult globin expression. Its broad expression pattern suggests a complex transcriptional regulation involving multiple, yet poorly defined, regulatory elements.

Using integrative *in silico* and chromatin accessibility analyses, here we identified an erythroid-specific enhancer located 52Kb upstream of the *NR2F2* transcription start site. This element shows epigenetic features of an active enhancer in K562 erythroid cells. Notably, in subclones derived from adult HUDEP2 erythroid progenitor cells that spontaneously re-express fetal gamma globin, *NR2F2* is reactivated, concomitantly with the opening of the -52Kb enhancer. We also identify the transcription factor ZBTB7A as a repressor of *NR2F2*, as knock-out of *ZBTB7A* in HUDEP2 cells restores *NR2F2* expression and active chromatin marks at the -52Kb region. Our findings uncover a novel distal enhancer controlling *NR2F2* expression in erythroid cells.