## Table S5. Gene functions and pathways associated with ancestral TFBS

| Factor | Biological Process | P-val | Fold | Biological pathways | P-val |
|---|---|---|---|---|---|
| ***CTCF*** | Positive regulation of branching involved ureteric bud morphogenesis (19 genes) | 9e-9 | 2.05x | Glycine betaine degradation (9 genes) | 1e-5 |
| | Renal vesicle development (13 genes) | 7e-8 | 2.21x | Folate transformations (9 genes) | 5e-4 |
| | Hindlimb morphogenesis (38 genes) | 2e-7 | 2.03x | Interleukin-6 signaling (8 genes) | 7e-4 |
| | Blood vessel endothelial cell migration (19 genes) | 2e-7 | 2.03x | Alpha6 beta4 integrin-ligand interactions (11 genes) | 2e-3 |
| ***GATA1*** | Mesonephros development (19 genes) | 1e-9 | 2.63x | TRAF6 mediated NF-kb activation (13 genes) | 2e-3 |
| | Cardiac ventricle development (67 genes) | 6e-4 | 2.13x | | |
| | Heart valve morphogenesis (17 genes) | 4e-8 | 2.99x | | |
| | Cardiac septum development (12 genes) | 8e-8 | 3.52x | | |
| ***MYC*** | Ribosome biogenesis (146 genes) | 4e-7 | 2.11x | HIF-a-alpha transcription factor network (80 genes) | 6e-6 |
| | Circadian rhythm (66 genes) | 2e-6 | 2.90x | BMAL1: CLOCK/NPAS2 activates gene expression (23 genes) | 5e-5 |
| | Regulation of transcription from RNA polymerase II promoter by nuclear hormone receptor (61genes) | 3e-4 | 2.04x | Circadian Clock (32 genes) | 2e-4 |
| | Cellular response to biotic stimulus (76 genes) | 6e-4 | 2.55x | Coregulation of androgen receptor activity (29 genes) | 5e-4 |
| ***SOX2*** | Dentate gurus development (9 genes) | 2e-7 | 2.25x | Validated nuclear estrogen receptor beta network (15 genes) | 1e-3 |
| | Central nervous system neuron axonogenesis (16 genes) | 1e-5 | 2.71x | | |
| | Nephron tubule morphogenesis (14 genes) | 3e-5 | 2.13x | | |
| | Erythrocyte development (22 genes) | 3e-5 | 2.84x | | |
| ***ETS1*** | Inner mitochondrial membrane organization (26 genes) | 2e-3 | 2.03x | N-glycan trimming in the ER and Calnexin/Calreticulin cycle (13 genes) | 2e-3 |
| | Peripheral nervous system neuron development (11 genes) | 3e-3 | 2.26x | Advanced glycosylation endproduct receptor signaling (23 genes) | 8e-3 |
| | | | | Recruitment of NuMA to mitotic centrosomes (12 genes) | 8e-3 |
| ***MAX*** | ATP hydrolysis coupled proton transport (31 genes) | 4e-5 | 4.35x | BMAIL1: CLODK/NPAS2 activates gene expression (23 genes) | 9e-6 |
| | Isoprenoid biosynthetic process (22 genes) | 4e-5 | 3.27x | Circadian clock (32 genes) | 5e-5 |
| | Cellular response to steroid hormone stimulus (50 genes) | 5e-5 | 2.42x | Transferrin endocytosis and recycling (27 genes) | 1e-3 |
| | Regulation of receptor biosynthesis process (16 genes) | 7e-5 | 3.33x | Transcription regulation of white adipocyte differentiation (69 genes) | 5e-3 |