FOXP2 Syndrome

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The transcription repressor FOXP2 is a crucial player in nervous system evolution and development of humans and songbirds. In order to provide an additional insight into its functional role we compared target gene expression levels between human neuroblastoma cells (SH-SY5Y) stably overexpressing

FOXP2

cDNA of either humans or the common chimpanzee, Rhesus monkey, and marmoset, respectively. RNA-seq led to identification of 27 genes with differential regulation under the control of human

FOXP2

, which were previously reported to have FOXP2-driven and/or songbird song-related expression regulation. RT-qPCR and Western blotting indicated differential regulation of additional 13 new target genes in response to overexpression of human

FOXP2.

These genes may be directly regulated by FOXP2 considering numerous matches of established FOXP2-binding motifs as well as publicly available FOXP2-ChIP-seq reads within their putative promoters. Ontology analysis of the new and reproduced targets, along with their interactors in a network, revealed an enrichment of terms relating to cellular signaling and communication, metabolism and catabolism, cellular migration and differentiation, and expression regulation. Notably, terms including the words "neuron" or "axonogenesis" were also enriched. Complementary literature screening uncovered many connections to human developmental (autism spectrum disease, schizophrenia, Down syndrome, agenesis of corpus callosum, trismus-pseudocamptodactyly, ankyloglossia, facial dysmorphology) and neurodegenerative diseases and disorders (Alzheimer's, Parkinson's, and Huntington's diseases, Lewy body dementia, amyotrophic lateral sclerosis). Links to deafness and dyslexia were detected, too. Such relations existed for single proteins (e.g., DCDC2, NURR1, PHOX2B, MYH8, and MYH13) and groups of

proteins which conjointly function in mRNA processing, ribosomal recruitment, cell-cell adhesion (e.g., CDH4), cytoskeleton organization, neuro-inflammation, and processing of amyloid precursor protein. Conspicuously, many links pointed to an involvement of the FOXP2-driven network in JAK/STAT signaling and the regulation of the ezrin-radixin-moesin complex. Altogether, the applied phylogenetic perspective substantiated FOXP2's importance for nervous system development, maintenance, and functioning. However, the study also disclosed new regulatory pathways that might prove to be useful for understanding the molecular background of the aforementioned developmental disorders and neurodegenerative diseases.