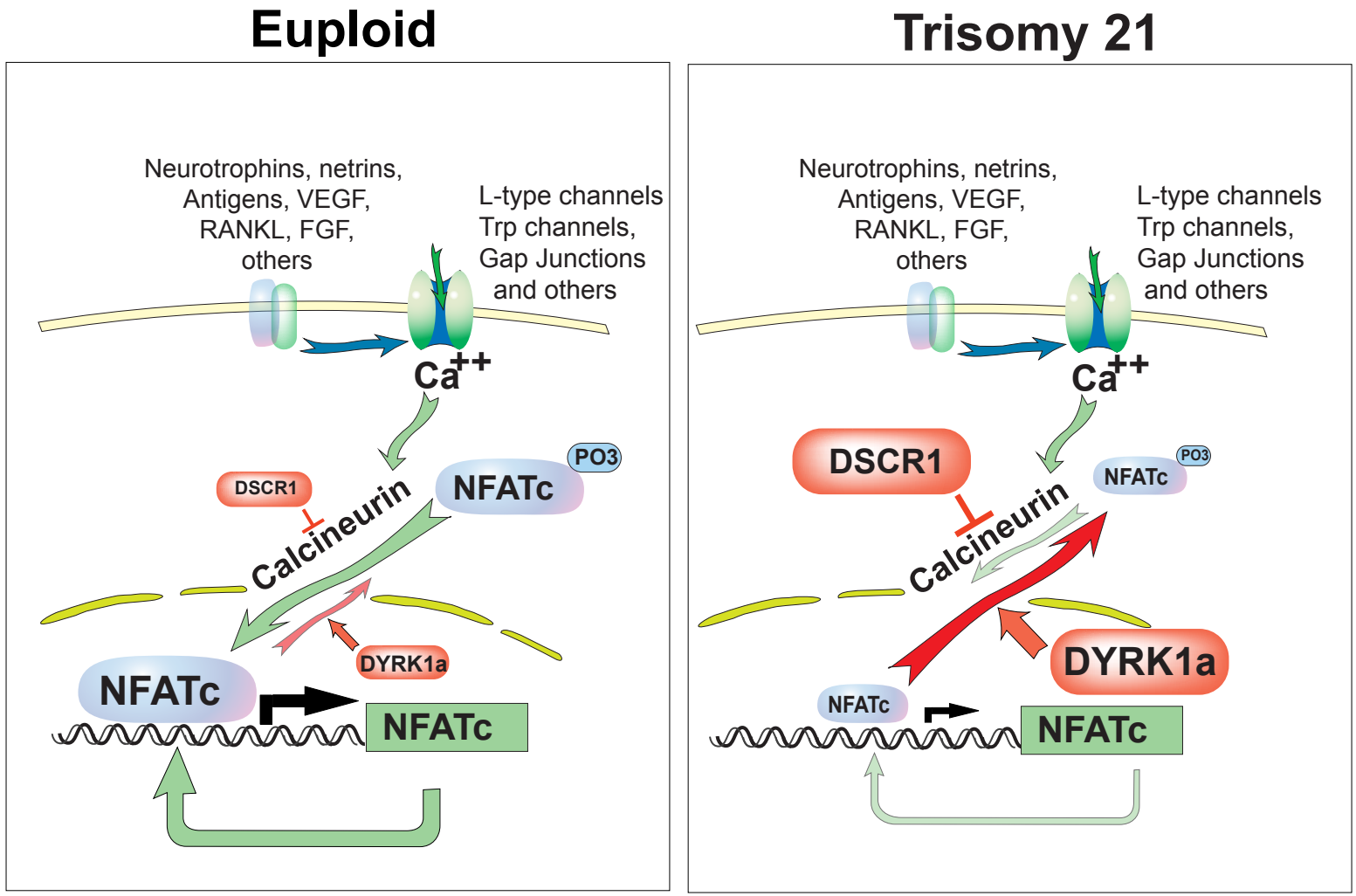
Increased Expression of DSCR1 and DYRK1a on Chromosome 21 Destabilizes the NFAT Genetic Circuit



Ca^{2+} entry through a variety of channels and mechanisms leads to activation of the calcineurin phosphatase and rapid dephosphorylation of the NFATc family and the exposure of nuclear localization sequences (for review see Refs 7,8, 23). DSCR1 also called MCIP1 or CSP1 inhibits calcineurin and prevents NFATc nuclear entry. Once in the nucleus NFATc family members are rapidly exported by the actions of the dual specificity kinase DYRK1a (minibrain), which primes these molecules for additional phosphorylation by GSK3.

We propose that in Down Syndrome a 1.5-fold increase in DSCR1 and DYRK1 both slows nuclear entry and accelerates nuclear exit of the NFATc family. This results in a reduction in NFATc activity. The reduction in NFATc nuclear occupancy is enhanced by the positive feedback loop regulating NFATc1 and c4. The prediction that the characteristics of Down syndrome are similar to weak NFATc phenoptyes is borne out by studies reported in this paper and in published work. Red depicts inhibitors of NFAT signaling while green depicts activators.