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P21. INCREASED DOSAGE OF THE BIFUNCTIONAL TRANSCRIPTION FACTOR ARX DISTURBS ITS TUNEABLE ACTIVITY AND MAY CAUSE NEURONAL DEFECTS

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Defective activity of dosage-sensitive transcription factors (TFs) has been established to change gene expression and cause a phenotypic effect during brain development. Aristaless-related homeobox protein (ARX) is a bifunctional transcription factor capable of activating or repressing gene transcription, whose mutations have been found in a wide spectrum of neurodevelopmental disorders including severe cortical malformations, refractory epileptic encephalopathy and Intellectual Disability (ID). Dosage sensitivity of ARX locus is an emerging question since it has been recently demonstrated that breakpoints in enhancer elements of ARX can alter its tissue-specific expression in the developing brain. On the other hand, the Xp21 region, where ARX maps, undergoes frequent genomic rearrangements detected in neurobehavioral phenotypes. Here we report that ARX is a dosage-sensitive gene whose protein acts as a concentration-dependent TF in the regulation of direct and indirect disease targets whose functioning is abolished by loss-of-function mutations in ARX. We further show that in an ID male patient carrying an extra-copy of ARX and its ultra-conserved enhancers, a strong increase in ARX dosage causes a deregulation in effector genes. In murine GABA-ergic oriented neurons, real-time PCR and western blot analysis reveals that under increased dosage conditions ARX causes a deregulation in key controllers of neuronal activity. Our results suggest that not only a reduction but also an extra dosage of ARX may disturb the tuneable bifunctional activity and thus produce cognition disorders.