Altered expression of neuropeptides in FoxG1-null heterozygous mutant mice.

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Abstract
Foxg1 gene encodes for a transcription factor essential for telencephalon development in the embryonic mammalian forebrain. Its complete absence is embryonic lethal while Foxg1 heterozygous mice are viable but display microcephaly, altered hippocampal neurogenesis and behavioral and cognitive deficiencies. In order to evaluate the effects of Foxg1 alteration in adult brain, we performed expression profiling in total brains from Foxg1+/− heterozygous mutants and wild-type littermates. We identified statistically significant differences in expression levels for 466 transcripts (P<0.001), 29 of which showed a fold change ≥1.5. Among the differentially expressed genes was found a group of genes expressed in the basal ganglia and involved in the control of movements. A relevant (three to sevenfold changes) and statistically significant increase of expression, confirmed by qRT-PCR, was found in two highly correlated genes with expression restricted to the hypothalamus: Oxytocin (Oxt) and Arginine vasopressin (Avp). These neuropeptides have an important role in maternal and social behavior, and their alteration is associated with impaired social interaction and autistic behavior. In addition, Neuronatin (Nnat) levels appear significantly higher both in Foxg1+/− whole brain and in hippocampal neurons after silencing Foxg1, strongly suggesting that it is directly or indirectly repressed by Foxg1. During fetal and neonatal brain development, Nnat may regulate neuronal excitability, receptor trafficking and calcium-dependent signaling and, in the adult brain, is predominantly expressed in parvalbumin-positive GABAergic interneurons. Overall, these results implicate the overexpression of a group of neuropeptides in the basal ganglia, hypothalamus, cortex and hippocampus in the pathogenesis FOXG1 behavioral impairments.
