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MOLECULAR STUDIES OF DYSLEXIA: REGULATION AND FUNCTION OF DYX1C1

av

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ABSTRACT

Developmental dyslexia is a specific reading disability characterized by unexpected difficulty in reading and writing despite adequate intelligence, education, normal senses and social environment. It is the most common childhood learning disorder affecting five to ten percent of school age children and it is more common among boys than girls. The core deficit in dyslexia is believed to involve phonological processing, the lowest level of the language system needed for reading. Dyslexia has a neurological basis demonstrated by anatomical and functional brain studies, in which differences have been found in the brains dyslexic readers compared to normal readers. Subtle disturbances in neuronal migration during early brain development have been suggested to be one of the mechanisms leading to dyslexia.

Dyslexia has a complex genetic basis which has been investigated by extensive family, twin- and molecular genetic studies. To date, many chromosomal loci, including the nine official dyslexia loci, have been linked to dyslexia, and a number of susceptibility genes within those regions have been identified. At least four of these candidate genes are involved in neuronal migration and brain development, otherwise their function it not well understood.

The aim of this thesis was to study the regulation and function of the first dyslexia susceptibility gene *DYX1C1*. The *DYX1C1* gene was identified when it was disrupted by a translocation segregating with dyslexia in one family. Since then, many association studies have supported its role in the etiology of dyslexia and general reading ability. In rodents, embryonic knockdown of Dyx1c1 results in deficits in neuronal migration leading to ectopias in the neocortex and hippocampus, and impairments in performing tasks related to learning and memory.

In Paper 1, we characterized three dyslexia associated single nucleotide polymorphims in the regulatory regions of *DYX1C1* and identified regulatory proteins binding to the genomic region upstream of the translation start site. We showed that these changes could have functional consequences and therefore could explain the association signal. In Papers II and III, we connected DYX1C1, both function and its regulation, to estrogen signaling. The expression of DYX1C1 increased after treatment with the steroid hormone, 17β-estradiol, which was due to the regulatory effect of the estrogen receptor β and TFII-I (III). Furthermore, we demonstrated that DYX1C1 interacts with the estrogen receptors α and β with functional consequences (II). In Paper IV, we scrutinized the function of DYX1C1 by characterizing the global gene-expression patterns after manipulating its expression levels in a neuroblastoma cell line and by identifying its protein interactions partners. By this means, we connected DYX1C1 to molecular pathways relevant to neuronal migration and nervous system development. For instance, the expression of neuronal migration genes RELN and DCX was changes after manipulating DYX1C1 levels. In addition, we studied the random cell migration of neuroblastoma cells after perturbation of DYX1C1 levels to confirm that the identified pathways and connections are functional. Indeed, DYX1C1 affects the velocity of the random cell migration and the protein domains in the C-terminus of DYX1C1 are needed for this.

From the findings in this thesis, we can conclude that DYX1C1 is involved in several interesting molecular pathways and we provide starting points for future studies. In addition, we strengthen and further develop some of the already existing hypothesis of the biological causes of dyslexia.

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