Neuroscience 324 (2016) 496–508

VISUAL IMPAIRMENT IN *FOXG1*-MUTATED INDIVIDUALS AND MICE

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Abstract—The *Forkead Box G1* (*FOXG1* in humans, *Foxg1* in mice) gene encodes for a DNA-binding transcription factor, essential for the development of the telencephalon in mammalian forebrain. Mutations in *FOXG1* have been reported to be involved in the onset of Rett Syndrome, for which sequence alterations of *MECP2* and *CDKL5* are known. While visual alterations are not classical hallmarks of Rett syndrome, an increasing body of evidence shows visual impairment in patients and in *MeCP2*and *CDKL5* animal models. Herein we focused on the functional role of FOXG1 in the visual system of animal models (*Foxg1*$^{+/Cre}$ mice) and of a cohort of subjects carrying *FOXG1* mutations or deletions. Visual physiology of *Foxg1*$^{+/Cre}$ mice was assessed by visually evoked potentials, which revealed a significant reduction in response amplitude and visual acuity with respect to wild-type littermates. Morphological investigation showed abnormalities in the organization of excitatory/inhibitory circuits in the visual cortex. No alterations were observed in retinal structure. By examining a cohort of *FOXG1*-mutated individuals with a panel of neuro-ophthalmological assessments, we found that all of them exhibited visual alterations compatible with high-level visual dysfunctions. In conclusion our data show that *Foxg1* haploinsufficiency results in an impairment of mouse and human visual cortical function. **© 2016 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: Rett syndrome, autism, west syndrome, visual cortex, inhibitory interneurons, cortical blindness.

INTRODUCTION

Rett Syndrome (RTT) is a neurodevelopmental disorder representing one of the most common causes of intellectual disability in girls. Beside the classical form due to *MECP2* mutations, two other forms have been associated to specific molecular defects, namely the early-onset seizure variant, mostly due to *CDKL5* mutations, and the congenital variant, mostly due to *FOXG1* mutations. The association between the *FOXG1* gene (OMIM#164874) and the congenital variant of RTT is relatively recent (Ariani et al., 2008), and since its discovery an increasing number of patients with *FOXG1* point mutations has been reported. The human *FOXG1* gene is located in the 14q12 chromosome and encodes for a phylogenetically well-conserved DNA-binding transcription factor of 489 aa. The mechanisms by which *FOXG1* mutations cause RTT are still unknown, however the presence of *FOXG1* on an autosomic chromosome suggests haploinsufficiency as a candidate for the aetiopathological mechanisms of this RTT variant (Shoichet et al., 2005; De Filippis et al., 2012). Furthermore, a physical interaction between MeCP2 and FOXG1 has been demonstrated (Dastidar et al., 2012) suggesting that, at least in the Central Nervous system (CNS), an impairment in FOXG1-MeCP2 interaction could be critical for the development of RTT. Intriguingly, a recent report indicates that Foxg1 displays, together with a nuclear localization, a specific targeting to mitochondria. This finding sheds new light on the etiology of FOXG1-RTT and on the original mitochondrial dysfunction hypothesis for the RTT pathogenesis (Pancrazi et al., 2015).

Foxg1 presence is essential for the embryonic development of the telencephalon in mammalian forebrain (Xuan et al., 1995). Its expression is abundant since the early development, persisting at lower levels in the adult cortex including the visual areas (Shen et al., 2006). This pattern suggests that specific aspects of the RTT associated with *FOXG1* mutations might involve visual cortical circuits. Foxg1 is also necessary for the correct formation of the inner ear and the olfactory system (Pauley et al., 2006; Duggan et al., 2008) and the appropriate crossing of retinal ganglion cell axons during

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Abbreviations: FOXG1, Forkead Box G1; GCL, ganglion cell layer; RBPMS, anti-RNA-binding protein; RTT, Rett Syndrome.

http://dx.doi.org/10.1016/j.neuroscience.2016.03.027
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