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Pleiotropic activities of the (atypical ?) kinesin KIF21B during cortical development

Par

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**Salle des Pas Perdus
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Abstract:

Cortical development progresses through concurrent steps, including neural proliferation, migration and differentiation, that rely on dynamic cell shape remodeling which largely depends on the tight regulation of the microtubules (MT) cytoskeleton. Mutations in tubulin, MT associated proteins or motors have been linked to several neurodevelopmental disorders including malformation of cortical development (MCDs), affecting 2,5% of the world population. Here we identified *KIF21B* gene as a major locus of human neurodevelopmental disorder. We identified 4 de novo variants in *KIF21B* gene in patients with intellectual disabilities associated with several brain malformations, including microcephaly, corpus callosum agenesis or facial dimorphism. In support of the pathogenic potential of the discovered alleles, expression of KIF21B variant in mice using in utero electroporation or in zebrafish embryos recapitulated key neurodevelopmental phenotypes, namely migration and microcephaly. In addition, longitudinal neuroanatomical analysis of *Kif21b* KO model showed strong morphological defects starting prenatally and worsening with time. Finally, we demonstrated that Kif21b regulates migration of projection neurons through the tight control of locomotion and neural shape. Although its motility is dispensable, the regulatory function cytoskeleton dynamics is essential for neuronal migration. Altogether, our data represent an important step to delineate the mechanisms involving KIF21B-mediated MT dynamics and trafficking in the context of brain development.

Selected publications:

1. Morelli G, Even A, Gladwyn-Ng I, Le Bail R, Shilian M, Godin JD, Peyre E, Hassan BA, Besson A, Rigo JM, Weil M, Brône B, Nguyen L., p27Kip1 Modulates Axonal Transport by Regulating α -Tubulin Acetyltransferase 1 Stability. *Cell Rep.* 2018 May 22;23(8):2429-2442
2. Broix L, Asselin L, Silva CG, Ivanova EL, Tilly P, Gilet JG, Lebrun N, Jagline H, Muraca G, Saillour Y, Drouot N, Reilly ML, Francis F, Benmerah A, Bahi-Buisson N, Belvindrah R, Nguyen L, Godin JD, Chelly J, Hinckelmann MV. Ciliogenesis and cell cycle alterations contribute to KIF2A-related malformations of cortical development. *Hum Mol Genet.* 2018 Jan 15;27(2):224-238.
3. Tielens S, Huysseune S, Godin JD, Chariot A, Malgrange B, Nguyen L. Elongator controls cortical interneuron migration by regulating actomyosin dynamics. *Cell Res.* 2016 Oct;26(10):1131-1148.
4. Godin JD, Creppe C, Laguesse S, Nguyen L. Emerging Roles for the Unfolded Protein Response in the Developing Nervous System. *Trends Neurosci.* 2016 Jun;39(6):394-404.
5. Laguesse S, Creppe C, Nedialkova DD, Prévot PP, Borgs L, Huysseune S, Franco B, Duysens G, Krusy N, Lee G, Thelen N, Thiry M, Close P, Chariot A, Malgrange B, Leidel SA, Godin JD, Nguyen L. A Dynamic Unfolded Protein Response Contributes to the Control of Cortical Neurogenesis. *Dev Cell.* 2015 Dec 7;35(5):553-567
6. Volvert ML, Prévot PP, Close P, Laguesse S, Pirotte S, Hemphill J, Rogister F, Kruzy N, Sacheli R, Moonen G, Deiters A, Merkenschlager M, Chariot A, Malgrange B, Godin JD, Nguyen L. MicroRNA targeting of CoREST controls polarization of migrating cortical neurons. *Cell Rep.* 2014 May 22;7(4):1168-83.