

## 論文の内容の要旨

# Molecular genetic study of the function of KIF3B in brain development

(脳の発達における KIF3B の機能に関する分子遺伝学的研究)

アルサバン アシュワック ハッサン エス

ALSABBAN ASHWAQ HASSAN S

Transport of *N-methyl-D-aspartate receptors* (NMDARs, NRs) is crucial for brain development and wiring. NMDA-dependent bidirectional synaptic plasticity is a key regulator for learning and memory process. For neuronal communication, synapse formation, remodelling and stabilization transactions (known as bidirectional synaptic plasticity) are critical and mediated by the regulation of NMDAR trafficking during development. KIF3B, a member of the kinesin molecular motor protein family (KIF), controls the plus-end-targeted transport of cargo along microtubules. Some KIF3B cargo, such as fodrin-associated vesicles, APC/PAR3 and N-cadherin/

$\beta$ -catenin vesicles, is essential for neurite formation, polarity and spine plasticity. Here, we show that KIF3B supports the transport of NMDA receptor subunit 2A (NR2A) and regulates the function of adenomatous polyposis coli (APC), which is essential for neuronal circuit formation in the brain. *Kif3b*<sup>+/-</sup> mutant mice exhibited a reduction in synaptic levels of NR2A due to a disturbance in NR2A transport and in those of NMDA receptor subunit 2B (NR2B) due to NR2B instability. These data indicate that genetic and cellular haploinsufficiency of KIF3B causes defects in NR2A transport and dysfunction of the APC-containing complex. This study provides strong evidence that KIF3B plays crucial roles in brain development. One of the most important roles of KIF3B is its modulation and maintenance of the formation of KIF3/APC complexes, leading to the effective transport of PSD95/NR2A vesicles, considered to be specific cargo of the KIF3/APC complex, along dendrites targeting activated (tagged) synapses. The second critical role of KIF3B in the mammalian brain is its regulation of the Wnt signalling pathway, which is critical for the formation of neuronal circuits and synaptic bidirectional plasticity.