論 文 審 査 の 結 果 の 要 旨

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（論文審査の結果の要旨）

The gene encoding IQ Motif and Sec7 Domain 2 (IQSEC2), located on the X-chromosome, has been linked to neurodevelopmental disorders, like intellectual disability, epilepsy, and certain forms of autism spectrum disorders (ASDs). IQSEC2 is a PSD-95 binding molecule and an ADP-ribosylation factor 6 (ARF6)-Guanidine Exchange Factor (Arf6-GEF) in the excitatory post synapse, where it contributes to receptor trafficking. Having generated a CRISPR/Cas9 system-based knockout (KO) mouse model of IQSEC2, I attempted to elucidate its function in behavior and synapse physiology. I observed the following major findings:

1. IQSEC2 KO mice exhibited autistic behaviors, including overgrooming, decreased social interaction, social preference, and social novelty preference.
2. Up-regulation of c-Fos expression in the medial prefrontal cortex (mPFC) by social stimulation was attenuated in IQSEC2 KO mice.
3. AMPAR, NMDAR, and GABAR-mediated synaptic transmissions were decreased in the pyramidal neurons in layer 5 of the mPFC in IQSEC2 KO mice.
4. The above synaptic phenotypes were attributable to the postsynaptic deletion of IQSEC2 from the result of cell type specific IQSEC2 KD using in utero electroporation.
5. Re-expression of IQSEC2 isoform 1 in the mPFC rescued the electrophysiological and behavioral phenotypes in IQSEC2 KO mice.

The committee chair and vice-chairs evaluated that the thesis deserved a doctoral dissertation.