1. No.
   2019G027

2. Title
   Study on the pathophysiological mechanism of SCA42 using nicotine-induced tremor model

3. Period
   2019-2023

4. Summary
   We identified *CACNA1G*, which codes for the T-type calcium channel Cav3.1, as the causative gene for spinocerebellar ataxia type 42 (SCA42). Tremor cases were observed in SCA42, and clinically, we found that zonisamide was markedly effective. In this study, we generated mutant Cav3.1 model mice and cells to elucidate the pathogenic mechanisms of mutant Cav3.1 and explore therapeutic approaches. Firstly, using CRISPR/Cas9, we created *Cacna1g* mutant mice with the same mutations as in humans and obtained findings that were behaviorally and pathologically consistent. Furthermore, in electrophysiological investigations, we demonstrated that the expression of mutant Cav3.1 in HEK293T cells resulted in a positive shift in voltage dependence, which could be restored by zonisamide. Next, we expressed mutant Cav3.1 in Neuro 2a cells and demonstrated that synaptic-related protein (PSD-95) exhibited mislocalization. We showed that the addition of zonisamide, mibefradil (Ca channel blocker), and nicotine improved this mislocalization. The possibility that mutant Cav3.1 causes transport disruption of PSD-95 and abnormal synaptic formation was suggested. We will further explore therapeutic approaches using stable Cav3.1-expressing cell lines (SH-SY5Y cells).