

Knockout of AGTPBP1, a gene for cerebellar ataxia, lead to neuronal death and increased dopaminergic release

Wang-Tso Lee

National Taiwan University Children 's Hospital, Taiwan



17th INTERNATIONAL CHILD
NEUROLOGY CONGRESS

INTRODUCTION

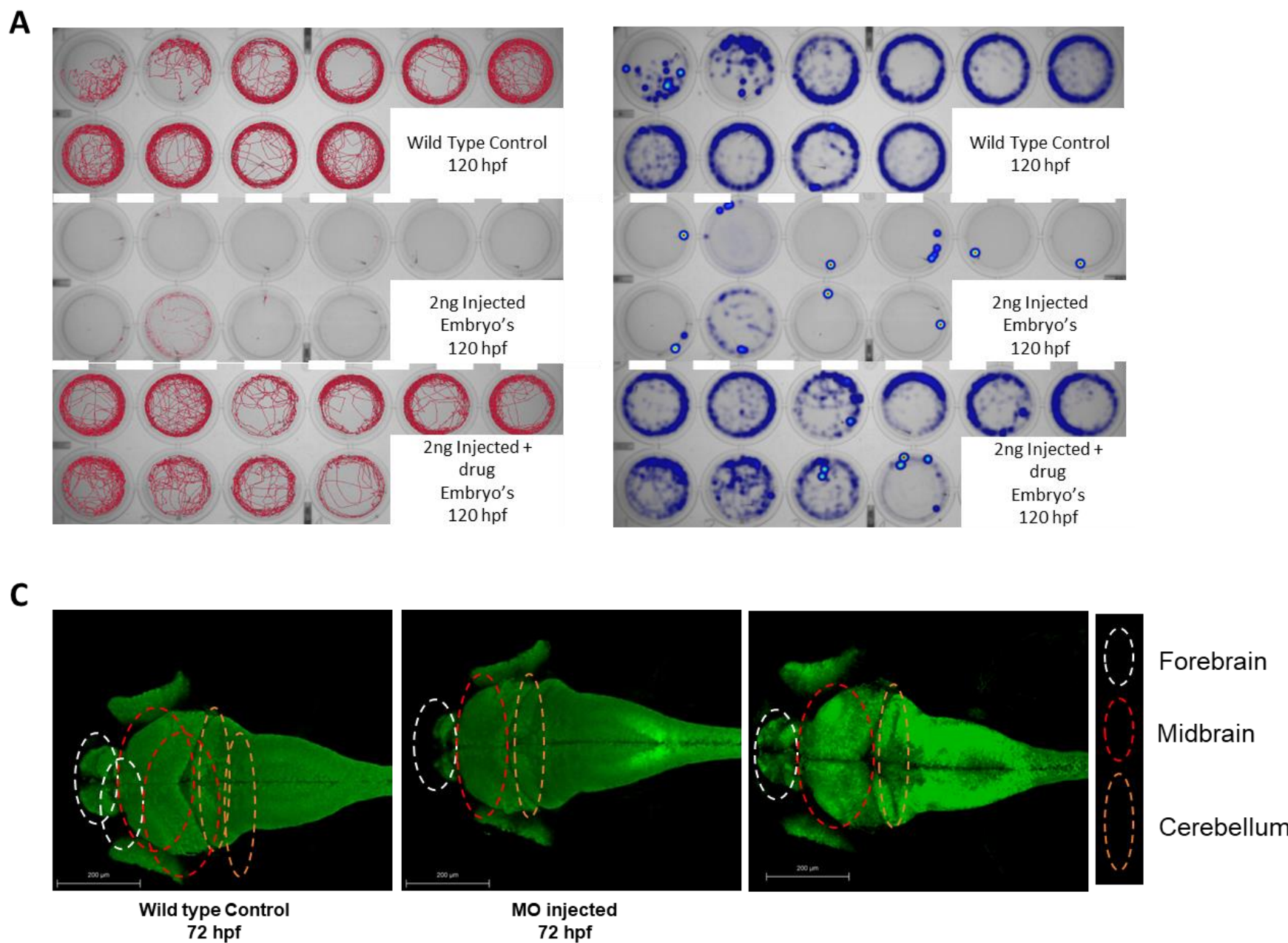
The genetic ataxias are clinically and genetically heterogeneous. Recently, AGTPBP1 was found to be associated with infantile-onset, progressive and frequently fatal neurodegeneration with cerebellar ataxia and atrophy. In our patients with cerebellar ataxia, we also found patients with AGTPBP1 mutation. AGTPBP1 mutations may have multiple mechanisms leading to cerebellar atrophy and neurological symptoms. But there is no new treatment for the patients.

OBJECTS

- To investigate the pathogenic mechanisms leading to neuronal death in AGTPBP1-related cerebellar ataxia.
- To search for new therapy for patients with AGTPBP1-related neuronal death.

MATERIALS and METHODS

We used both in vitro and in vivo zebrafish model to investigate possible pathogenic mechanisms of AGTPBP1 mutation on neuronal development, and search for potential treatment for these patients in the future. The effect of AGTPBP1 knockout on neuronal proliferation, differentiation, and neurite formation were investigated.



RESULTS

We found that knockout of AGTPBP1 lead to decreased proliferation and differentiation. Knockout of AGTPBP1 also lead to elongation of neurites. In addition, knockout of AGTPBP1 also lead to increased expression of tyrosine hydroxylase and dopa decarboxylase, and increased release of dopamine. Cell survival assay showed that knockout of AGTPBP1 increased the susceptibility of neurons to glutamate toxicity although the expression of NMDAR1 was downregulated. Knockout of AGTPBP1 also increased the production of ROS and increased mitochondrial depolarization, which may lead to more cell death. In vivo model using zebrafish also showed change of behavior and reduced cerebellum, forebrain, and midbrain in AGTPBP1 knockdown.

CONCLUSIONS

Knockout of AGTPBP1, a gene for cerebellar ataxia, may lead to increased cell death and dopamine release. The in vivo zebrafish model also showed impaired movement behavior and reduced brain volume. After treatment with medication X, it lead to improve in swimming behavior and also increase brain volume. It indicates that the new treatment may be helpful for the patients. Further clinical trial may be indicated.

CONTACT

Wang-Tso Lee, MD, PhD
wangtslee@ntu.edu.tw

