Identification of a polyglutamine protein aggregation inhibitor QAI1 and its therapeutic effects on polyglutamine neurodegenerative diseases.

Yoshitaka Nagai[1,2,3], Eiko N. Minakawa[3], H. Akiko Popiel[3], Hiroshi Yamane[3], Masayoshi Tada[4], Toshiaki Takahashi[4], Toshihide Takeuchi[1,3], Hideki Mochizuki[2], Tatsushi Toda[5], Keiji Wada[3], Osamu Onodera[4]

[1]Dept. Neurotherapeutics, Grad. Sch. Med., Osaka Univ., [2]Dept. Neurology, Grad. Sch. Med., Osaka Univ., [3]Dept. Degener Neurol Dis, Natl Ctr Neurology&Psychiatry, [4]Dept. Neurology, Brain Res. Inst., Niigata Univ., [5]Dept. Neurology, Grad. Sch. Med., Univ. Tokyo

The polyglutamine (polyQ) diseases, including Huntington's disease and spinocerebellar ataxias (SCAs), are a group of inherited neurodegenerative diseases which are caused by an abnormal expansion of the glutamine-encoding CAG repeat in each causative gene. The expansion of the polyQ stretch triggers abnormal β-sheet conformational transition and aggregation of polyQ-containing proteins, leading to neurodegeneration. Toward developing therapy for polyQ diseases, we performed a high-throughput screening of a large small chemical compound library for polyQ aggregation inhibitors using an *in vitro* turbidimetric aggregation assay. As a results, we identified PolyQ Aggregation Inhibitor 1 (QAI1), which is a clinically-approved drug and is known to cross the blood-brain barrier. We revealed QAI1 exerts its anti-aggregation property by inhibiting the upstream toxic β-sheet conformational transition of polyQ proteins. QAI1 was shown to suppress polyQ aggregation and neurodegeneration in *Drosophila* models of polyQ diseases. Most importantly, we successfully demontrated that oral administration of QAI1 ameliorates the motor dysfunction in two polyQ disease model mice. Furthermore, QAI1 exerted its therapeutic effects even when administered after the symptom onset. We are currently planning a clinical trial to investigate the efficacy of QAI1 as a disease-modifying therapeutic candidate for polyQ disease patients.