Intracerebroventricular AAV injection of human UBE3A recovers deficits in a mouse model for Angelman syndrome.

Melinda M. Peters¹, Rebekah L. Cook¹, Kelsey Magolan¹, Hayden E. Greene¹, Bianca M. Capraro¹, Jodi Cook², Mark Pykett², Edwin J. Weeber¹ Kevin R. Nash¹
¹ Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, Florida, United States of America
² PTC Therapeutics Incorporated, South Plainfield, New Jersey, United States of America

Angelman syndrome is a rare neurological genetic disorder caused by loss of maternal expression of the UBE3A allele in the brain. Angelman syndrome primarily affects the central nervous system; and individuals with the condition have severe intellectual disabilities, seizures, difficulty speaking, and ataxia. UBE3A encodes for the protein E6AP, an E3 ubiquitin ligase. A unique feature of this gene is that it undergoes maternal imprinting in a neuron-specific manner. In the majority of Angelman syndrome cases, there is a mutation or deletion in the maternally inherited UBE3A gene. Currently, no treatment for this disorder exists. The nature of Angelman syndrome as a single gene disorder suggests there is a potential for rescue by using a gene therapy approach. In the current study, we examined viral gene delivery of the human UBE3A gene into the CNS of a mouse model for Angelman syndrome using recombinant adeno-associated virus. This approach has the advantage of offering long-term protein expression, low immunogenicity, neuronal transduction, and has shown efficacy in multiple clinical trials.