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A Novel Adeno-Associated Virus Capsid with Enhanced Neurotropism Corrects a Lysosomal Transmembrane Enzyme Deficiency

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Recombinant adeno-associated viruses (AAVs) are popular *in vivo* gene transfer vehicles. However, vector doses needed to achieve therapeutic effect are high and some target tissues in the central nervous system remain difficult to transduce. Gene therapy trials employing AAV for the treatment of neurological disorders have seldom led to demonstrated clinical efficacy. Important contributing factors are low transduction rates and inefficient distribution of the vector. To overcome these hurdles, a variety of capsid engineering methods have been utilized to generate capsids with improved transduction properties. Here we describe an alternative approach to capsid engineering, which draws on the natural evolution of the virus and aims to yield capsids that are better suited to infect human tissues. We generated an AAV capsid to include amino acids that are conserved among natural AAV2 isolates and tested its biodistribution properties in mice and rats. Intriguingly, this novel variant, AAV-TT, demonstrates strong neurotropism in rodents and displays significantly improved distribution throughout the central nervous system as compared to AAV2. Additionally, subretinal injections in mice revealed markedly enhanced transduction of photoreceptor cells when compared to AAV2. Importantly, AAV-TT exceeds the distribution abilities of benchmark neurotropic serotypes AAV9 and AAVrh10 in the central nervous system of mice, and is the only virus, when administered at low dose, that is able to correct the neurological phenotype in a mouse model of mucopolysaccharidosis IIIC, a transmembrane enzyme lysosomal storage disease, which requires delivery to every cell for biochemical correction. These data represent unprecedented correction of a lysosomal transmembrane enzyme deficiency in mice and suggest that AAV-TT based gene therapies may be suitable for treatment of human neurological diseases such as mucopolysaccharidosis IIIC, which is characterised by global neuropathology.