Drug Discovery Tool Aimed at Gene Splicing Correction

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Technology description

Researchers at the Research Institute have developed a stably transfected cell line that expresses wild type survival motor neuron gene-2 (SMN2) that can be used as a drug discovery tool aimed at gene splicing correction. SMN2 is a potential therapeutic target for Proximal Spinal Muscular Atrophy (SMA), an autosomal recessive neuromuscular disease. SMA is caused by a homozygous loss of the SMN1 gene. Humans have two nearly identical SMN genes, SMN1 and SMN2. The SMN2 generates a truncated protein due to a C to T nucleotide alteration in exon 7, which leads to inefficient RNA splicing of exon 7. Stable cell lines expressing SMN2 minigene have been generated that allow for detection of correct splicing of the SMN2 gene.

Benefit Analysis

Spinal muscular atrophy is a devastating motor neuron disease caused by a missing or mutated gene (SMN1) which leads to spinal motor neuron atrophy and muscle weakness. This muscular weakness leads to severe disability and the possibility of premature death in most people that are afflicted with the disease. SMA is the primary genetic cause of infant mortality in the United States. It is estimated that there are 25,000 Americans living with this disease, and that around 1 in 6000 to 1 in 10,000 infants are born annually worldwide with SMA. Most infants born with severe SMA die within 2 years according to the National Institute of Health's National Institute of Neurological Disorders and Stroke.

Application area

Since the SMN2 is nearly identical to SMN1, it has the potential to rescue the disease phenotype if it is corrected. Incorrect splicing of the SMN2 gene is thought to be responsible for its inability to produce sufficient SMN protein to compensate for the lack of SMN1 gene expression in SMA patients. Therefore a therapeutic method that stimulates SMN2 gene expression would benefit SMA patients. The HEK293T cell line that expresses the SMN2 minigene would be useful as:

a drug discovery tool to look at compounds or methods to correct the splicing of the SMN2 gene

Advantages

Unique because it contains the human SMN2 genomic fragment containing exons 6 through 8, including the intronic sequences. Other SMN2 minigenes do not contain intron 6 or exon 8 in the

proper configuration and therefore are not a proper model for the normal endogenous splicing activity of SMN2.
Has a FLAG sequence that allows for detection of splicing events and the testing of therapies that correct the SMN2 splicing

Institution

The Research Institute at Nationwide Children's Hospital