A STUDY OF CRE-II TRANSCRIPTION FACTOR IN THE PROMOTER REGION OF THE SMN2 GENE

RESEARCH CENTRE: Human Genome Centre, School of Medical Sciences, USM

CURRENT STATUS OF PROJECT: Ongoing

RESEARCHERS:

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TRACK RECORD: Understanding The role of SMN1 and NAIP genes in the Pathogenesis of Spinal Muscular Atrophy (SMA) Patients in Malaysia (2003-2005)

INTRODUCTION:

Spinal Muscular Atrophy (SMA) is classified into 3 groups which are Type I (severe), Type II (intermediate) and Type III (mild). The levels of SMN expression driven by SMN2 in motor neurons are inversely correlate with the severity of the disease. This was suggested by the finding of an increased copy number of SMN2 in patients with a milder disease. Attempts will be made that SMN2 acts as a modifying gene in SMA. Presence of any extra copies of the SMN2 gene helps to reduced the severity of this disease. Therapeutic strategy could be done through the 'induction of the SMN2 transcription' by activation of the SMN2 promoter. Mutations, which disrupt the cis-elements in the SMN2 promoter region called the cyclic-AMP response element (CRE-II) will reduce the transcriptional activity while duplication of CRE-II may increase it. The most critical transcriptional factor can thus be identified and leads to an effective therapy of SMA.

OBJECTIVES:

1. To clone the SMN2 gene and to study the expression of SMN2 gene in SMA patient.
2. To correlate the effect of mutation in the promoter region of the SMN2 gene and its gene expression.

METHODOLOGY:

The SMN2 gene promoter region of the Type I and Type III patients with two SMN2 copies will be PCR-amplified and mutation screening will be done using the dHPLC. Those promoter regions will be sequenced and compared. Luciferase reporter vectors with the SMN2 promoter regions will be transfected into COS7 cell lines. A comparison of final SMN2 gene expression between the recombinant construct will be measured using luminometer.

EXPECTED OUTCOME:

This study will create better understanding about the transcriptional control of the promoter region in SMN2 gene. It can help to identify the most critical transcriptional factor, eventually establishing an effective gene therapy of SMA. Also findings from this study will be published in peer-reviewed scientific journal.