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Review

Implications of the Transgenic/Knockout Mouse Model of Human Spinal Muscular Atrophy

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A mouse model for human spinal muscular atrophy (SMA) has recently been established by crossing mouse lines carrying a knockout mutation of the mouse *Smn* gene with transgenic mouse lines that express the human centromeric *SMN* (*SMN2*) gene. These SMA-like mice similar to SMA patients show pathological changes in the spinal cord and skeletal muscle, as well as in expression of the *SMN2* gene. The severity of the pathology in these mice is correlated with the amount of intact SMN protein in spinal cord. These mice clearly demonstrate that the telomeric *SMN* (*SMN1*) gene is responsible for SMA and should be useful in elucidating the molecular mechanisms of the *SMN* gene and in the design of therapeutic protocols for SMA patients.

Proximal spinal muscular atrophy (SMA) is an autosomal recessive disease characterized by degeneration of the anterior horn cells of the spinal cord leading to muscular paralysis with muscular atrophy. Clinical diagnosis of SMA is based on progressive symmetric weakness and atrophy of the proximal muscles. Affected individuals are clinically categorized into three types according to the age of onset and progression of the disease. Children with type I (acute) SMA (also known as Werdnig-Hoffmann disease) are most severely affected. They usually show SMA symptoms before 6 months of age and typically die within the first 2 years. Types II and III (chronic) SMA are milder forms with onset of symptoms varying between 6 months to 17 years of age.[1-3] Together they comprise the second most common fatal autosomal recessive disease, with a carrier rate of 1% - 3% in the general population and an incidence of 1 in 10,000 newborns.[4-6]

Positional cloning strategies led to the identification of the survival motor neuron (*SMN*) gene as the candidate gene for SMA.[7] Only deletions or intragenic mutations in the telomeric copies of this gene (*SMN1*) result in an SMA phenotype, whereas mutations in the centromeric of this gene (*SMN2*) show no clinical consequence, providing further evidence that *SMN1* is associated with SMA.[8-10] Both the *SMN1* and *SMN2* genes produce a full-length SMN transcript of nine exons encoding 294 amino acids. The SMN2 gene is

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