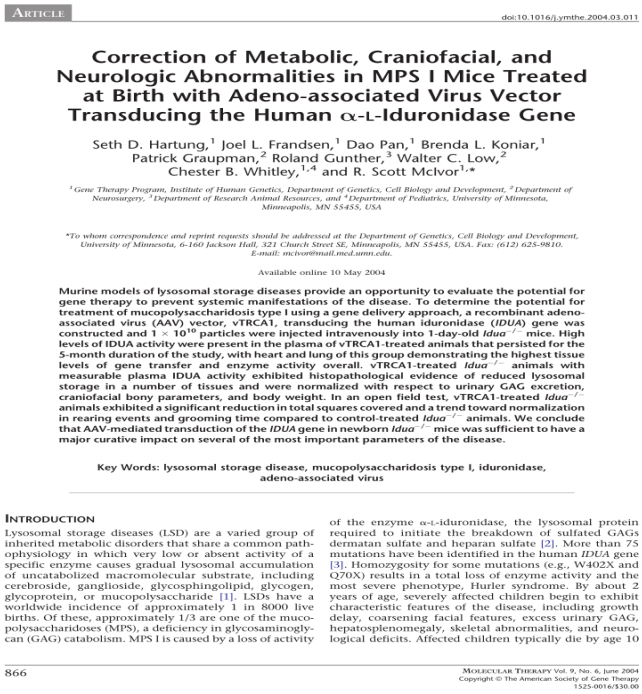
McKusicks Heritable Disorders Of Connective Tissue



ARTICLE

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Correction of Metabolic, Craniofacial, and Neurologic Abnormalities in MPS I Mice Treated at Birth with Adeno-associated Virus Vector Transducing the Human α-L-Iduronidase Gene

Seth D. Hartung,[1] Joel L. Frandsen,[1] Dao Pan,[1] Brenda L. Koniar,[1] Patrick Graupman,[2] Roland Gunther,[3] Walter C. Low,[2] Chester B. Whitley,[1,4] and R. Scott McIvor[1,*]

[1] Gene Therapy Program, Institute of Human Genetics, Department of Genetics, Cell Biology and Development, [2] Department of Neurosurgery, [3] Department of Research Animal Resources, and [4] Department of Pediatrics, University of Minnesota, Minneapolis, MN 55455, USA

*To whom correspondence and reprint requests should be addressed at the Department of Genetics, Cell Biology and Development, University of Minnesota, 6-160 Jackson Hall, 321 Church Street SE, Minneapolis, MN 55455, USA. Fax: (612) 625-9810. E-mail: mcivor@mail.med.umn.edu.

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Murine models of lysosomal storage diseases provide an opportunity to evaluate the potential for gene therapy to prevent systemic manifestations of the disease. To determine the potential for treatment of mucopolysaccharidosis type I using a gene delivery approach, a recombinant adeno-associated virus (AAV) vector, vTRCA1, transducing the human iduronidase (*IDUA*) gene was constructed and 1×10^{10} particles were injected intravenously into 1-day-old *Idua*$^{-/-}$ mice. High levels of IDUA activity were present in the plasma of vTRCA1-treated animals that persisted for the 5-month duration of the study, with heart and lung of this group demonstrating the highest tissue levels of gene transfer and enzyme activity overall. vTRCA1-treated *Idua*$^{-/-}$ animals with measurable plasma IDUA activity exhibited histopathological evidence of reduced lysosomal storage in a number of tissues and were normalized with respect to urinary GAG excretion, craniofacial bony parameters, and body weight. In an open field test, vTRCA1-treated *Idua*$^{-/-}$ animals exhibited a significant reduction in total squares covered and a trend toward normalization in rearing events and grooming time compared to control-treated *Idua*$^{-/-}$ animals. We conclude that AAV-mediated transduction of the *IDUA* gene in newborn *Idua*$^{-/-}$ mice was sufficient to have a major curative impact on several of the most important parameters of the disease.

Key Words: lysosomal storage disease, mucopolysaccharidosis type I, iduronidase, adeno-associated virus

INTRODUCTION

Lysosomal storage diseases (LSD) are a varied group of inherited metabolic disorders that share a common pathophysiology in which very low or absent activity of a specific enzyme causes gradual lysosomal accumulation of uncatabolized macromolecular substrate, including cerebroside, ganglioside, glycosphingolipid, glycogen, glycoprotein, or mucopolysaccharide [1]. LSDs have a worldwide incidence of approximately 1 in 8000 live births. Of these, approximately 1/3 are one of the mucopolysaccharidoses (MPS), a deficiency in glycosaminoglycan (GAG) catabolism. MPS I is caused by a loss of activity of the enzyme α-L-iduronidase, the lysosomal protein required to initiate the breakdown of sulfated GAGs dermatan sulfate and heparan sulfate [2]. More than 75 mutations have been identified in the human *IDUA* gene [3]. Homozygosity for some mutations (e.g., W402X and Q70X) results in a total loss of enzyme activity and the most severe phenotype, Hurler syndrome. By about 2 years of age, severely affected children begin to exhibit characteristic features of the disease, including growth delay, coarsening facial features, excess urinary GAG, hepatosplenomegaly, skeletal abnormalities, and neurological deficits. Affected children typically die by age 10

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