

## Candidate Diseases for Gene Therapy

Disease	Defect	Incidence	Target Cells
<b>Genetic</b>			
Severe combined immunodeficiency (SCID/ADA)	Adenosine deaminase (ADA) in ~25% of SCID patients	Rare	Bone marrow cells or T cells
A	Factor VII deficiency	1:10,000 males	Liver, muscle, fibroblasts, or bone marrow cells
B	Factor IX deficiency	1:30,000 males	
Familial hypercholesterolemia	Deficiency of low-density lipoprotein (LDL) receptor	1:1 million	Liver
Cystic fibrosis	Faulty transport of salt in lung epithelium. Loss of <i>CFTR</i> gene	1:3,000 whites	Airways in the lungs
Hemoglobinopathies: thalassemias/sickle cell anemia	Structural defects in $\alpha$ - or $\beta$ -globin gene	1:600 in certain ethnic groups	Bone marrow cells, giving rise to red blood cells
Gaucher disease	Defect in the enzyme glucocerebrosidase	1:450 in Ashkenazi Jews	Bone marrow cells, macrophages
$\alpha_1$ -Antitrypsin deficiency: inherited emphysema	Lack of $\alpha_1$ -antitrypsin	1:3,500	Lung or liver cells
<b>Acquired</b>			
Cancer	Many causes, including genetic and environmental	1 million/y in US	Variety of cancer cell types; liver, brain, pancreas, breast, kidney
Neurologic diseases	Parkinson's, Alzheimer's, spinal cord injury	1 million Parkinson's and 4 million Alzheimer's patients in US	Direct injection in the brain, neurons, glial cells, Schwann cells
Cardiovascular	Restenosis arteriosclerosis	13 million in US	Arteries, vascular endothelial cells
Infectious diseases	AIDS, hepatitis B	Increasing numbers	T cells, liver, macrophages

From Verma IM, Somia N. Gene therapy: promises, problems, and prospects. *Nature* 1997;389:240.

## Changes in Bone Mineral Density, Body Composition, and Lipid Metabolism During Growth Hormone (GH) Treatment in Children With GH Deficiency

Adults with childhood-onset growth hormone deficiency (GHD) have reduced bone mass, increased fat mass, and disorders of lipid metabolism. The aim of the present study was to evaluate bone mineral density (BMD), bone metabolism, body composition, and lipid metabolism in GHD children before and during 2 to 3 years of GH treatment. The mean age of the 40 children participating in this study of bone metabolism and body composition was 7.9 years. An additional 17 GHD children participated in the study of lipid metabolism. Lumbar spine BMD, total body BMD, and body composition were all measured with dual energy X-ray absorptiometry. Volumetric BMD (or bone mineral apparent density [BMAD]) was calculated to correct for bone size. Standard deviation scores (SDS) were used to compare with normative data.

Lumbar spine BMD, total body BMD, and BMAD were all decreased at baseline. All these BMD variables increased significantly during treatment. The Table (page 14) presents the effects at various time points. Lean tissue mass SDS

increased continuously. Fat mass SDS decreased markedly during the first 6 months and remained stable thereafter. The chemical parameters of bone formation and resorption at baseline did not differ from those of normals and then increased during the first 6 months of treatment. Serum 1,25 dihydroxyvitamin D increased continuously during treatment, whereas parathyroid hormone and serum calcium remained stable. The lipid profile was normal at baseline.

The authors conclude that children with GHD have decreased bone mass. BMD, together with height and lean tissue mass, increased during treatment, which also had a beneficial effect on lipid metabolism.

Boot A, et al. *J Clin Endocrinol Metab* 1997;82:2423-2428.

**Editor's comment:** This interesting paper adds further data supporting the importance of GH treatment for GHD children, promoting linear growth and regulating different metabolic pathways. All patients presented in this study

## Mean of Different Variables at Baseline and During Growth Hormone Therapy

Variable	Baseline n = 38	At 6 Months GH Therapy n = 37	At 1 Year GH Therapy n = 33	At 2 Year GH Therapy n = 33
Lumbar spine BMD SDS	-1.62	-1.33 <sup>a</sup>	-0.98 <sup>a</sup>	-0.64 <sup>a</sup>
Lumbar spine BMAD SDS	-0.51	-0.50	-0.37	-0.19 <sup>a</sup>
Total body BMD SDS	-0.94	-1.35 <sup>b</sup>	-1.02	-0.61 <sup>b</sup>
Bone mineral content SDS	-2.29	-2.36	-1.52 <sup>a</sup>	-1.24 <sup>a</sup>
Lean tissue mass SDS	-2.72	-1.86 <sup>a</sup>	-1.53 <sup>a</sup>	-1.14 <sup>a</sup>
Fat mass SDS	-0.02	-0.59 <sup>c</sup>	-0.31 <sup>c</sup>	-0.59
% Body fat SDS	0.93	-0.39 <sup>a</sup>	-0.10 <sup>a</sup>	-0.45 <sup>c</sup>
Height SDS	-2.98	-2.32 <sup>a</sup>	1.86 <sup>a</sup>	-1.63 <sup>a</sup>
Body mass index SDS	0.45	0.24	0.39	0.37

<sup>a</sup>  $P < 0.001$ ; <sup>b</sup>  $P < 0.02$ ; <sup>c</sup>  $P < 0.01$  compared to baseline.

BMAD, bone mineral apparent density

BMD, bone mineral density

SDS, standard deviation score

From Boot A, et al. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. *J Clin Endocrinol Metab* 1997;82:2425. ©The Endocrine Society.

showed evidence of the anabolic effect of GH, as demonstrated by the increase in BMD, the increase in lean body mass, and the decrease in body weight. Some of these metabolic effects may be considered direct effects of GH replacement. An increase in the serum 1,25 dihydroxyvitamin D level has been reported during GH treatment due to renal inactivation induced by insulin-like growth factor 1, an indirect effect resulting in the beneficial increase in BMD.

The authors concluded that treatment had a beneficial effect on lipid metabolism. However, there were no significant changes found in lipid metabolism as baseline values were all normal. In my opinion, no conclusions can be drawn from the present study regarding the beneficial effects on lipid metabolism. Long-term studies in children need to be done since adults with GHD are at risk of hypercholesterolemia and coronary heart disease.

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### Growth Hormone Therapy in Prepubertal Children With Noonan Syndrome: First Year Growth Response and Comparison With Turner Syndrome

The authors report that during the first year of administration of recombinant human growth hormone (rhGH; 0.15 U/kg/d given by daily injection) to 23 prepubertal subjects with Noonan syndrome ( $9.4 \pm 3.0$  years), the increase in height velocity was 8.5 cm, approximately twice the pre-treatment growth rate. In a group of females with Turner syndrome of similar age at initiation of rhGH, the mean height increment was 8.1 cm during the first year of treatment. Four of 23 Noonan syndrome subjects had no significant change in height standard deviation scores (SDS) during rhGH administration. In Noonan patients, the in-

crement in height velocity during rhGH administration was directly related to birth weight, suggesting that low-birth-weight children with Noonan syndrome responded less well to treatment. The changes in bone age, growth velocity, and height SDS were similar in Turner and Noonan syndrome groups. The authors conclude that the linear growth response to short-term administration of rhGH is comparable in patients with Noonan and Turner syndrome.

De Schepper J, et al. *Acta Paediatr* 1997;68:943-946.