

Short Stature in Carriers of Recessive Mutation Causing Familial Isolated Growth Hormone Deficiency

The phenotype in patients with isolated GH deficiency (IGHD) type 1B is identical to patients with IGHD type 1A, which results from homozygous absence of the *GH-1* gene. Patients with type 1B have a loss of function mutation in the *GH-1* gene. Both 1A and 1B patients initially respond favorably to rhGH. However, they differ in that type 1A patients develop GH antibodies that then inhibit growth. Patients with type 1B do not develop GH antibodies and continue to respond.

These investigators report that family members who were heterozygous for the loss-of-function gene are frequently shorter than their homozygous normal relatives for the *GH-1* gene.

The authors studied an extended, interrelated Bedouin family with a G to C transversion at the 5th base in intron IV of *GH-1*, leading to loss of a splice site and utilization of a cryptic splice site in exon IV that resulted in loss of 73 bp and a nonfunctional 196 amino acid product. Among a sample of 50 first- and second-degree relatives of the 9 homozygous patients, 33 were found to be heterozygous for the *GH-1* mutation and 17 to be homozygous normals. The heterozygous subjects were significantly smaller than the normal individuals (-1.67 vs -0.40 SDS; $P > 0.05$) without relation to sex or age. In 33% of the heterozygous group, heights were ≥ 2 SDS below the mean (Tables 1 and 2). Stimulated secretion of GH was normal in the heterozygous subjects tested.

The authors *hypothesized* that this mutation impaired transport of the product to the secretory granules and that there was subnormal spontaneous GH secretion. They concluded that the described mutation manifested itself as short stature in heterozygous subjects and suggested that this or similar mutations in *GH-1* in the heterozygous state might account for some of the phenotypic variability in population heights and for some of the patients with normal short stature encountered in the clinic.

Leiberman E, et al. *Am J Med Genet* 2000;90:188-192.

Table 1
Mean Standard Deviation Scores for Height in Heterozygotes and Normal Homozygotes According to Sex

| | Heterozygotes Mean SDS (\pm SE) n | Normal Homozygotes Mean SDS (\pm SE) n | P |
|---------|--|---|-------|
| Males | -1.22 (\pm 0.28) n = 13 | -0.10 (\pm 0.19) n = 11 | NS |
| Females | -1.97 (\pm 0.29) n = 20 | -0.95 (\pm 0.31) n = 6 | NS |
| Total | -1.67 (\pm 0.21) n = 33 | -0.40 (\pm 0.19) n = 17 | <0.05 |

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Editor's comment: Limited clinical manifestations of rather severe autosomal recessive disorders are being recognized with increasing frequency. Some heterozygous relatives of patients with loss-of-function mutations of the GH receptor or of the GH-releasing hormone receptor may be inappropriately small, and occasional adult females who are heterozygous for loss-of-function mutations of CYP21B may manifest evidence of mild hyperandrogenism. The findings here may be of great significance in explaining some of the variation of stature that is seen in families.

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Table 2
Mean Height (cm) and Mean Standard Deviation Scores (MSDS) for Height in Heterozygotes (H) Compare With Normal Homozygotes (N) According to Age Groups

| | Adults | | Adolescents | | Children | |
|-------------|---------------|---------------|---------------|---------------|---------------|---------------|
| | H n = 19 | N n = 6 | H n = 5 | N n = 5 | H n = 9 | N n = 6 |
| Height | 158.6 | 169.3 | 143.4 | 157.4 | 105.2 | 126.5 |
| (\pm SE) | (\pm 0.57) | (\pm 1.51) | (\pm 2.41) | (\pm 2.63) | (\pm 2.53) | (\pm 2.45) |
| MSDS | -1.43 | -0.21 | -2.22 | -0.90 | -1.88 | -0.18 |
| (\pm SE) | (\pm 0.23) | (\pm 0.24) | (\pm 0.67) | (\pm 0.38) | (\pm 0.51) | (\pm 0.32) |

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