

References

1. Hirschhorn NJ et al. Genomewide linkage analysis of stature in multiple populations reveals several regions with evidence of linkage to adult height. *Am J Hum Genet* 69:106-110, 2001.
2. Perola M et al. Quantitative-trait-locus analysis of body-mass index and of stature, by combined analysis of genome scans of five Finnish study groups. *Am J Hum Genet* 69:117-123, 2001.

Editor's Comment: An additional comment is pertinent to this topic. Many genes known to influence stature have been identified by searching for disease genes. Examples include genes that harbor mutations that cause chondrodysplasias and many other syndromes associated with short stature. They range from homeobox-containing genes such as *SHOX* to cartilage matrix protein genes, i.e., *COL2A1* to transcription factor and receptor genes such as *SOX9* and *FGFR3*, respectively. Similarly, mutations of *Fibrillin 1* lead to tall stature in the Marfan syndrome. It seems likely that

there are genes that influence stature that are not associated with disease. The approach used here should identify genes in both categories. It will be interesting to see what genes fall into the latter category.

These papers are the first reported genome-wide studies of genetic linkage and stature. They probably represent the tip of the iceberg in terms of what will come as genetic markers become more dense, more populations are studied and analytical approaches become more sophisticated. As noted by Hirschhorn et al, identifying the genetic basis of variation in height raises important ethical issues as the potential for genetic engineering evolves. However, as they point out, a greater understanding of this subject could be beneficial in the contexts of establishing diagnoses and predicting adult stature of "short" children.

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Short Stature Homeobox-Containing Gene Deletion: Screening by Fluorescence in Situ Hybridisation in Patients with Short Stature

In an attempt to determine when to screen for *SHOX* gene deletion in subjects with short stature, Müsebeck and colleagues determined the frequency of *SHOX* deletions in 50 children with short stature. All children studied had a height < -2 SDS and 3 of the subjects also had the Madelung deformity (shortening and bowing of the radius with dorsal subluxation of the distal ulna and partial foreleg anomalies). Thirty-five of the 50 subjects had idiopathic short stature (ISS) accompanied by the absence of skeletal, endocrine, or organic symptoms and had no family history of short stature. Twelve subjects had upper limb abnormalities such as cubitus valgus. Two subjects had Léri-Weill dyschondrosteosis, and 3 had a congenital heart defect. Blood was analyzed by FISH process (Fluorescence In Situ Hybridization) for the *SHOX* deletion.

Microdeletions of the *SHOX* gene were not detected in any of the 35 patients with ISS. Of the 12 patients with additional upper limb abnormalities 5 (41.7%) displayed *SHOX* signals on only one sex chromosome. Of the 7 with short stature who displayed *SHOX* signals on 2 sex chromosomes, 3 had Madelung deformity and brachymetacarpia was present in the other 4. Point mutations of course are not picked up in the FISH technique. Molecular genetic methods will possibly detect point mutations in patients such as the 7 referred to above. Three patients with congenital heart defects did not carry *SHOX* deletions.

The authors state that their findings provide important guidelines for selecting patients for *SHOX* analysis. They

state that children with ISS are unlikely to carry such a mutation of the *SHOX* gene. Indeed, other studies have shown the *SHOX* mutation in about 1% of all patients with ISS. The combination of short stature and skeletal abnormalities of the forearm, however, makes the *SHOX* mutation much more probable. The authors caution that a father carrying a *SHOX* mutation on the X chromosome could transmit these mutations to his son because of crossing over between the pseudoautosomal regions of the X and Y chromosomes during paternal meiosis.

Müsebeck J, et al. *Eur J Pediatr* 2001;160:561-565.

Editor's Comment: *SHOX* gene deletion determinations have become increasingly popular in endocrine/genetic clinics evaluating children with short stature. Although, the number of subjects studied by Müsebeck et al is relatively small (n=50), their data are convincing. Apparently, *SHOX* gene determinations have little place in the evaluation of the child with ISS and should be reserved for those children who have deformities of the upper extremities even when those are very mild. Hopefully, data can be pooled in the future from numerous centers so that definitive guidelines for evaluation of *SHOX* gene determinations are more clearly defined.

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