

Administration of rosiglitazone, an inhibitor of peroxisome proliferator-activated receptor- γ which is an essential element for adipogenesis, increased adiponectin tissue mRNA values and also serum levels. Serum glucose was decreased as were serum levels of insulin.

In other mouse models of obesity (e.g. leptin receptor deficiency), administration of adiponectin lowered blood glucose and insulin values. In another mouse model, a lipodystrophic mouse without fat, serum concentrations of adiponectin were undetectable. Hyperglycemia and hyperinsulinemia were present. Administration of adiponectin lowered serum glucose and insulin levels. Both leptin and adiponectin were required in the lipotrophic mice to restore serum glucose and insulin values to normal.

In the article by Berg et al, serum glucose concentrations were decreased with the administration of recombinant adiponectin to wild type, leptin deficient, and insulin deficient mice. Berg et al also demonstrated that adiponectin depressed hepatic glucose output in vitro which is thus the second physiological effect that might contribute to enhanced insulin sensitivity. In

calorically restricted wild type mice, serum adiponectin concentrations were twice those of freely feeding animals suggesting that this adipokine may be important in prolonging the lives of such animals.

Thus, the data in these manuscripts indicate that adiponectin plays a key role in energy metabolism. It enhances insulin sensitivity by lowering serum and tissue triglyceride values, by uncoupling of oxidative phosphorylation in muscle, and by suppressing hepatic glucose output. In addition to the effects on energy metabolism, adiponectin depresses the inflammatory response that accompanies atherogenesis. Indeed, patients with coronary artery disease have lower plasma adiponectin concentrations than do controls. Adiponectin inhibits inflammation in part by suppressing proliferation of myelomonocytic progenitor cells by accelerating apoptosis. The potential utilization of adiponectin as a therapeutic agent for patients with obesity, diabetes mellitus types 1 and 2, hyperlipidemia, and/or atherogenic disorders is clearly enormous. A lead article regarding Adipose Tissue as an Endocrine Gland will appear soon in GGH.

Allen Root, MD

Genetic Basis of Stature – Genome-Wide Search for Genes that Influence Normal Adult Height

It is well known that short parents have short children and vice versa, and that variation in normal stature has a strong genetic component. However, despite many decades of interest in the genetics of stature, the relevant genes remain elusive. In fact, the genetics of most common traits and diseases in humans is not well understood. The principal explanation is that the geneticist's primary tool for mapping genes is of only limited power for finding genes that have modest effects, such as those that contribute to common diseases and variable traits such as stature. Recent advances in genomics, however, have made it feasible to apply genome-wide linkage analysis to such entities. Indeed, the group led by Eric Lander has used this approach to identify genetic linkage for adult height.¹

In total, 2,327 individuals from 483 families were studied. Fifty-eight families resided in the Botnia region of Finland, 183 families were from other areas of Finland, 179 families were from southern Sweden and 63 families were from the Saguenay-Lac-St-Jean region of Quebec. They were originally ascertained to investigate other genetic traits. Males were older than 23.5 years and females older than 21.1 years to exclude individuals still growing. The original genotyping results that were based on average spacing of microsatellite markers from 6.5 cM to 12.5 cM depending on the study population, were reanalyzed using the variance-components method

implemented in the GENE-HUNTER 2 protocol. The method uses nonparametric multipoint approaches to generate LOD scores for chromosomal locations that reflect the likelihood that genotype data being observed is due to linkage relative to the absence of linkage.

Evidence for linkage was detected in four instances. A LOD score of 3.85 was obtained for linkage at chromosome 6q24-25 in Botnia. A score of 3.40 was calculated for a marker located at 7q31.3-36 in Sweden. A LOD score of 3.35 was determined for markers at 12p11.2-q14 in Finland and a score of 3.56 was found in Finland for 13q32-33. The authors note that a companion study also detected linkage at chromosome 7 site.²

The authors are optimistic that they have identified chromosomal regions where genes that influence stature reside, especially on chromosome 7. However, they caution that definitive interpretation is difficult in the absence of confirmation of linkage in additional populations. They observe their results were inconsistent across the four study groups, but note that this is typical in linkage studies of common diseases. They discuss possible reasons for the inconsistency including variation in sampling, existence of genetic variation in different populations and statistical fluctuations and false positives due to unknown causes.

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.

William Horton, MD

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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