

miscarried in the first trimester. There was an increased occurrence of prematurity, and 1 neonate died as a result of placental abruption. The mean singleton birth weight was at the 47th percentile, and the mean singleton birth length was at the 57th percentile. Forty percent of births were by cesarean section, which is comparable to other in vitro fertilization (IVF) studies. There were 6 infants with birth defects: 1 with a unilateral transverse limb reduction (amniotic band syndrome); 1 with neonatal seizures who had 3 cerebral infarcts on imaging; 1 with a minor hemangioma; 1 with minor strawberry hemangiomas on both arms; 1 with thickening of the tricuspid valve that did not require surgery; and 1 with bilateral webbed toes. Only 1 child of the 44 who had been followed up to 6 months of age was reported to have developmental delay. This was 1 of twins who had had no perinatal complications. This child had speech delay and was receiving speech therapy. This frequency of birth defects is certainly not out of line of what would be expected.

The financial cost of PGD by PBR is reported to be \$8500 for 1 typical cycle. Diagnostic testing for mendelian traits may involve as much as another \$1000 in laboratory costs.

The authors point out that in addition to the financial costs, there are some intrinsic risks of multiple gestations and the complications associated with them. Nevertheless, polar body prenatal diagnosis does provide families with another option in terms of prenatal diagnosis.

Strom CM, et al. *Pediatrics* 2000;106:650-653.

Table
Summary of Preimplantation Genetics
Pregnancies

Number of Fetuses	Number of Pregnancies	Number of Spontaneous Abortions	Number of Live Births
1	80	5	75
2	9	1	16
3	7	0	18*
5	1	1	0
Total	97	7	109

*Three couples had reduction to twins; 4 couples delivered triplets.

Reprinted with permission from Strom CM, et al. *Pediatrics* 2000;106:650-653

Editor's comment: The data from this large center are reassuring. The reliability of testing for mendelian disorders needs further study since there are really only 18 cases. The procedure certainly allows individuals to obtain a diagnosis before implantation, if that fits with their particular ethical stance. Clearly, the cost is much higher than that associated for prenatal diagnosis which is performed later in pregnancy. However, it does not involve termination of pregnancy, and only those embryos which do not have a detectable abnormal test would be used for implantation. The reader may wish to extend his/her knowledge of this alternative diagnostic technique as it undoubtedly will become a common tool of IVF.

Judith G. Hall, OC, MD

Spectrum of the Tricho-Rhino-Phalangeal Syndromes

Three types of tricho-rhino-phalangeal syndrome (TRPS) have been clinically defined. The features characterizing these syndromes, but described initially in TRPS I, include sparse, slowly growing scalp hair; sparse eyebrows laterally; bulbous tip of the nose; protruding ears; brachydactyly and mild to moderate short stature; and the presence of cone-shaped epiphyses of the middle phalanges on X-ray films. TRPS II is distinguished from TRPS I by the occurrence of exostoses; mental retardation often is present. TRPS III is distinguished by the greater severity of the characteristics of TRPS I.

Mutations of a gene designated *TRPS1*, which encodes a zinc finger transcription factor, were recently identified in patients with TRPS I. Microdeletions of chromosome 8q24.1 that include both *TRPS1* and *EXT1*, the gene mutated in hereditary multiple exostoses type I, are responsible for TRPS II. The current study by Lüdecke et al was done to determine if TRPS III is due to *TRPS1* mutations, representing the severe end of a clinical spectrum of TRPS I, or, alternatively, results from mutations of another gene. The results confirmed the former possibility and demonstrated a correlation between the type of mutation and the severity of clinical phenotype.

TRPS1 was screened by direct sequencing of the coding and flanking intron sequences for mutations in 79 patients with TRPS, including 57 unrelated individuals with either TRPS I or

TRPS III. Thirty-five different mutations were found in 44 of 51 unrelated patients. The majority were deletions or disruptions, nonsense and splicing mutations. These would be expected to truncate the transcription factor protein, leading to loss of function, since the resulting proteins would lack a nuclear localization signal needed for nuclear entry and the C-terminal zinc finger domain required for dimerization. These mutations would, therefore, act through haploinsufficiency. Missense mutations were identified in 8 cases. They all mapped to exon 6, which encodes the GATA zinc finger domain necessary for DNA binding. The resulting proteins would be expected to enter the nucleus and form complexes with other transcription factors that would function poorly because of defective DNA binding. They are predicted to exert a dominant negative effect, which as a disease-causing mechanism generally has a greater impact than haploinsufficiency.

The patients also were evaluated clinically, mainly in terms of height and severity of brachydactyly as judged from hand X-rays films. The results showed a continuous spectrum of severity. They further revealed that nonsense and disruption mutations, which would be predicted to cause haploinsufficiency of *TRPS1*, were associated with the range of severity typical of TRPS I. In contrast, the missense mutations predicted to act in a dominant negative fashion correlated with the severe end of the spectrum characteristic of TRPS III.

Thus, *TRPS1* mutations account for TRPS. Loss of function of 1 *TRPS1* allele gives rise to mild to moderate manifestations associated with the diagnosis of TRPS I. Missense mutations that act in a dominant negative manner account for the severe features observed in TRPS III. Chromosomal deletions that cause haploinsufficiency of *TRPS1*, *EXT1*, and potentially other neighboring genes are responsible for TRPS II.

Lüdecke H-J, et al. *Am J Hum Genet* 2001;68:81-91.

Editor's comment: This study nicely demonstrates how different types of mutations of the same gene can produce clinical phenotypes that appear to be different. The authors acknowledge that no mutations were detected in a few patients, making it possible that 1 or more other genes could harbor mutations that lead to a TRPS clinical phenotype. However, their conclusion that *TRPS1* is the major, if not only, gene locus responsible for this constellation of features cannot be disputed. It will be interesting to learn the function of *TRPS1* in skeletal growth and maturation.

William A. Horton, MD

BMI in Childhood and Its Association With Height Gain, Timing of Puberty, and Final Height

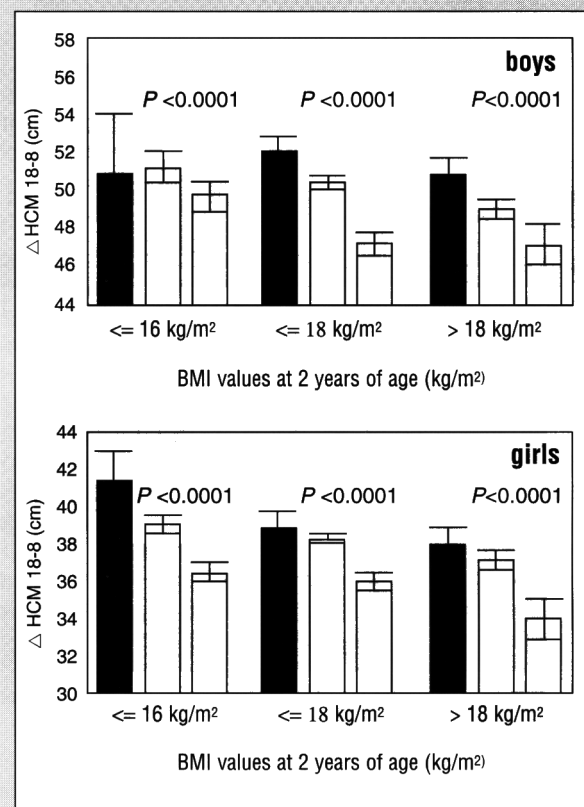
This study was undertaken to ascertain the effects of overnutrition in childhood on height, final height, and timing of puberty. This study was performed in 5111 grade-school children born in the early 1970s in Goteborg, Sweden. The final analysis was made in 3650 full-term healthy children whose growth information was accurate from birth to 18 years of age. The others were eliminated from the final analysis due to a variety of factors and/or illnesses. A computer-generated growth chart was produced for each child, and their nutritional status was assessed by body mass index (BMI) changes between 2 and 8 years of age. Mean parental heights were adjusted to assess genetic influences of the linear growth. Childhood BMI gain was related to an increased height gain during the same period (ie, an increase of 1 BMI unit was associated with an excess increase in height gain of 0.23 cm in boys and 0.29 cm in girls). The BMI also was linked to an earlier onset of puberty; the impact on the timing of puberty was 0.6 years in boys and 0.7 years in girls. Each increased unit of BMI gain in childhood also reduced the height gain in adolescence by 0.88 cm for boys and 0.51 cm for girls. However, no direct effect was found between childhood BMI gain and final adult height. The authors conclude that overnutrition between 2 and 8 years of age may lead to earlier onset of puberty and earlier achievement of adult height, but not greater height.

He Q, Karlberg J. *Pediatr Res* 2001;49:244-251.

Editor's comment: Overnutrition and/or obesity in childhood is a worldwide health concern because it may produce several adverse physical and psychosocial developmental consequences. Moreover, the obese child is at a higher risk of remaining obese throughout adulthood. Several studies have shown that overnutrition accelerates linear growth. This large population study certainly adds support to this concept. However, postnatal linear growth is complex, resulting from genetic, nutritional, and endocrine system influences. The BMI does not necessarily represent the only variable affecting growth, nor does it represent the true nutritional status of an individual. The effect of dietary attempts to lose weight was not investigated in this study. Usually, children who are obese tend to be on and off diets. This may lead to poor nutrition and potential growth deceleration. However, it is reassuring to know that this large population of obese children did not experience a reduction in final adult height.

Fima Lifshitz, MD

Figure
The Mean and Its 95% Confidence Interval of Δ HCM 18-8 for Boys and Girls in 3 Different Groups of BMI Values at 2 Years of Age



The cut off points, 16 and 18 kg/m², represent the 25th and 75th centile values at 2 years of age. Within each BMI group at 2 years, the values of height gain between 8 and 18 years are also shown separately in 3 childhood BMI change groups. The P values refer to the ANOVA to compare the differences in central tendency of height gain among the 3 BMI change groups.

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