

Editor's Comment: *These authors presented some truly encouraging information for endocrinologists to share with their patients with TS. Indeed hormone replacement therapy is associated with normal uterine development while the age of starting hormone replacement therapy is not a critical factor. Thus those women with TS who wish to participate in oocyte donation programs should be encouraged to do so or may be encouraged to do so with reasonably good assurance that their uterus should*

be capable of sustaining a normal pregnancy. As the authors noted, their study could have unexpected biases due to its cross-sectional nature.

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References

1. Doerr HG, Bettendorf M, Hauffa BP, et al. Hum Repro. 2005;20:1418-21.
2. Karnis MF, Zimon AE, Lalwani SI, et al. Fertil Steril. 2003;80:498-501.

GH Treatment Effects on Body Composition in SGA

The use of growth hormone (GH) therapy in small for gestational age (SGA) children with short stature, now approved and licensed both in the US and Europe, requires critical appraisal. Body composition in childhood may be affected by alteration of fetal growth. SGA infants who show catch-up growth tend to become obese and may be at risk for metabolic syndrome in adult life. However, SGA children who remain short are thin and have a low BMI and possibly compromised bone mineral density. The group of 25 SGA subjects (birth weight and current height <-2 SD) reported in this study were prepubertal and randomized to receive either GH therapy ($n=16$) or act as untreated controls for 3 years and then start GH therapy ($n=9$). Heights in both groups were <-2 SD and the daily GH dose was 1 mg/m² body surface area.

Clinical characteristics were comparable in the 2 groups. In the untreated subjects lean body mass (LBM) decreased during the 3 years ($P<0.01$) contrasting with the GH-treated group which showed catch-up increase of LBM. When the untreated subjects started GH, their LBM SDS also increased significantly. Therefore GH therapy, in the dose described, induced catch-up of LBM. However percentage body fat decreased in the GH-treated subjects. Bone mineral density SDS

measured by DEXA increased significantly in the GH-treated group compared to the untreated subjects.

Willemsen RH, Arends NJ, Bakker-van Waarde WM, et al. Long-term effects of growth hormone (GH) treatment on body composition and bone mineral density in short children born small-for-gestational-age: six-year follow-up of a randomized controlled GH trial. Clin Endocrinol (Oxf). 2007;67:485-92.

Editor's Comment: *These findings are of interest, but their clinical relevance remains uncertain. The anabolic effects of GH on muscle bulk and bone mineralization are demonstrated, as is its lipolytic effect. However the benefit to the child of these changes is difficult to assess. Is the improvement in BMD really going to prevent development of osteoporosis and increased fracture risk in adult life? The answers are unknown. Is the reduced LBM in the untreated short SGA child actually a disadvantage to the child? Again we are not certain. However, in this report the carefully studied longitudinal changes in body composition which occur during GH therapy are useful in documenting the anabolic and lipolytic effects of GH in short SGA children.*

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Widespread Monoallelic Expression of Human Autosomal Genes

With certain exceptions, it is generally assumed that maternally and paternally-derived copies (alleles) of each gene are expressed at comparable levels in humans. The first exception is inactivation of most of the genes residing on the X-chromosome in females—so called X-inactivation. Half of the cells in an embryo on average randomly inactivate the paternal X chromosome and half inactivate the maternal X chromosome around the time of implantation. The second exception involves imprinting of autosomal genes, such as IGF-2, on a parent-of-origin basis. A third exception is a small group of autosomal genes that are subject to random monoallelic expression; these include genes encoding odorant receptors, T cell receptors, interleukins, and natural killer cell receptors. There is new evidence that monoallelic expression of autosomal genes may be

much more extensive than previously believed.

Gimelbrant et al exploited the growing number of single nucleotide polymorphisms (SNPs) and advances in gene chip (array) technology to survey allele-specific transcription of about 4,000 genes in lymphoblastoid cell lines from 3 individuals. They took advantage of the observation that once a cell decides to express one of 2 alleles, the clonal descendants of this cell continue to express the selected allele. Since lymphoblastoid cells are polyclonal, they were able to derive clonal B cell lines using single-cell cloning.

To perform the genome-wide screen for monoallelic transcription, the investigators developed protocols to distinguish polymorphic allele expression based on detection of SNPs in nuclear RNA, which is enriched in intronic RNA, where most SNPs associated

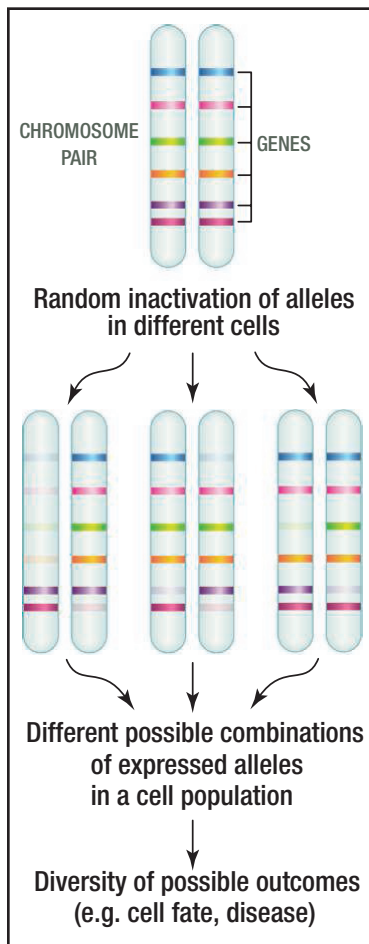
with genes reside. Conversion of this RNA to double-stranded cDNA and analysis on a SNP array generated “transcriptosome-derived genotypes” that allowed monoallelic expression to be identified. Filters were used to minimize cDNA genotyping artifacts. About 10% of SNPs were reliably called from this analysis, which was expected since most of the other SNPs are likely present in regions of the genome that are not expressed by B cell lines that were studied.

As proof-of-concept, the investigators first showed that random inactivation of X-chromosome genes could be detected in the clonal cell lines and then demonstrated as an example of their approach that monoallelic expression of the amyloid precursor protein gene could be detected. They next turned to genome-wide screening.

On the array used for analysis, there were SNPs present for ~11,000 genes. They were able to detect allele-specific transcription for ~4,000 genes in 2 or more cell clones. Of the ~4,000 genes examined, 2.2% were detected as monoallelically expressed with multiple informative SNPs per gene per clone. An additional 7.3% of assessed genes were identified as monoallelically expressed based on a single informative SNP per gene per clone. The genes included both B cell-specific genes and ubiquitously expressed genes. The investigators suggested a conservative estimate that over 1,000 genes are subject to random monoallelic expression in humans.

Several interesting observations were made. For example, the choice of expressed allele was made independently for each gene within a given clonal cell line. This is in contrast to the chromosomal-wide coordination characteristic of X-inactivation. Another finding was that a disproportionately large fraction of genes coding for cell surface proteins—transmembrane receptors and surface proteins was detected.

The authors concluded by suggesting that at least 1,000 human genes display random monoallelic transcription



Generating diversity. Alleles are randomly inactivated on a pair of chromosomes in a human somatic cell. The various patterns of inactivation in progeny cells are then stabilized (epigenetically). This can generate diverse cellular and physiological outcomes. Reprinted with permission Ohlsson R. Science. 2007;318:1077-8. Copyright © 2007 AAAS. All rights reserved.

that could contribute to genetic diversity within tissues of an individual as well as between individuals. A commentary by Ohlsson¹ notes that although monoallelic expression has been known in humans, this study by Gimelbrant expands the concept further especially by documenting it in a much larger number of genes than previously appreciated. He briefly discusses possible mechanisms that could account for the phenomenon as well as its potential role in modulating disease (Figure).

Gimelbrant A, Hutchinson JN, Thomson BR, Chess A. Widespread monoallelic expression of human autosomes. Science. 2007;318:1136-40.

Editor's Comment: This is one of several publications in recent years that challenges what we were taught about mendelian genetics. Of note, several genes relevant to human growth disorders were identified as displaying monoallelic expression including the growth hormone receptor gene (GHR) and genes that harbor mutations responsible for Ellis van Creveld syndrome (EVC) and the trichorhinophalangeal syndrome 1 (TRPS1). It seems quite plausible that monoallelic expression of these genes could contribute to the clinical variability of these conditions.

Lymphoblastoid cells have very different functions compared to chondrocytes, osteoblasts and other cells that contribute to skeletal growth; and their patterns of gene expression may differ dramatically. Screening the latter cells for monoallelic transcription would be technically much more difficult than for lymphoblastoid cells, but it would likely reveal monoallelic expression of additional growth related genes.

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Reference

1. Ohlsson R. Science. 2007;318:1077-8.

Stroke, Cardiac Disease and Diabetes Mellitus in Hypopituitarism

The impact of long-term growth hormone deficiency (GHD) and of long-term growth hormone (GH) treatment on cerebrovascular and cardiovascular diseases and diabetes mellitus is unknown. Holmer et al evaluated

the incidence of nonfatal stroke and cardiac events and the prevalence of type 2 diabetes mellitus (T2DM) in a cohort of GHD patients and healthy controls. The authors also studied the effects of cardioprotective drugs and 6