

pediatric endocrinologists and geneticists than the article by Hunter, as it deals with limb lengthening. He presents the historical aspects and then presents a concise summary of Ilizarov's contributions in the 1980s. The Verona surgeons have now described their results in 230 tibial lengthenings by monolateral fixation performed between 1990 and 1995; 58 were in ACH patients. Using these data, he points out that 40 days in a fixator was required for 1 cm of lengthening, or 200 days for 5 cm. The complication rate is now much less than previously, and Aldegheri reports (J Bone Joint Surg [Am] 1999;81:624-634) that only 7% of patients had complications undergoing lengthening with his latest modification in technique. Gross points out that physical and mental scores for adults with ACH do not differ from the general population until

about age 40, when back pain, weakness, and arthritis become disabling. Whether the effect of leg lengthening will speed up or delay this process in ACH, or adversely affect hip anatomy and function, remains unknown. Gross also comments:

If tibial lengthening is successful in a patient with ACH, treatment remains incomplete until the femur and humerus have also been successfully lengthened. The financial and physical costs are substantial and there simply is no follow-up information to justify routine lengthening of several long bones. Thus, despite the gratifying improvements, the results of these procedures still need long-term evaluation and review.

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Russell-Silver Syndrome Begins to Be Unraveled

Russell-Silver syndrome is a very common diagnosis associated with intrauterine growth retardation.¹ However, it has become clear that it is a heterogenous disorder. Approximately 10% of cases have been associated with maternal uniparental disomy for chromosome 7. This observation suggests there are genes on chromosome 7 that are imprinted. *MEST* (also known as *PEG1*) is an imprinted gene expressed only from the paternal allele, which maps to human chromosome 7q.² Thus, patients who have maternal uniparental disomy lack paternal activation of the gene.

Lefebvre and coworkers disrupted the murine homologue, *Mest*, by gene targeting in embryonic stem (ES) cells.² The targeted gene was imprinted and reversibly silenced by passage through the female germ line. Paternal transmission activated the allele and caused embryonic growth retardation. Interestingly, *Mest*-deficient females showed abnormal maternal behavior, including impaired placentophagia. Thus, in mice, both growth and behavior are affected.

Interestingly, imprinting of *PEG1/MEST* is lost in lymphocytes and transformed lymphoblastoid cell lines. This is not entirely surprising since genomic imprinting is usually regulated in a tissue-specific way. In addition, imprinting may be controlled in a promoter-specific way such that promoters allow expression from a particular parental allele.³ Imprinting can be governed in an isoform-specific way such that a single transcription unit will encode for different proteins via alternative splicing. Kosaki et al⁴ demonstrate that there are different isoforms in lymphoblastoid tissue where isoform 1 is expressed only from the paternal allele while there is biallelic expression of isoform 2. Interestingly, there may be differences in mouse and human expression of isoforms, again in a tissue-specific way.

In addition to the paternally expressed *PEG1/MEST* gene in the 7q32 region, there also is a *g2-COP* gene⁵ with biallelic expression in fetal brain and liver and in adult peripheral blood, and monoallelically paternal expression in other fetal tissues, including the skeleton, muscle, skin, kidney, adrenal glands, placenta, intestine, lung, chorionic plate, and amnion. Absence of paternal *g2-COP* transmission during embryonic development may contribute to the Russell-Silver phenotype. It may well be that other imprinted genes are present in this chromosome region. However, the expression is clearly under tight

control in terms of tissue specificity and time of expression in development.

Duplication of 7p11.2-p13 also has been described as resulting in the Russell-Silver phenotype. The report by Monk et al¹ describes a chromosomal duplication within the region where gene *GRB10* (growth factor receptor-binding protein 10) has been identified. This suggests that Russell-Silver syndrome could result from overexpression of a maternally expressed imprinted gene as well as absence of a paternally expressed gene.

1. Monk D, et al. *Am J Hum Genet* 2000;66:36-46.
2. Lefebvre L, et al. *Mest*. *Nat Genet* 1998;20:163-169.
3. Lefebvre L, et al. *Peg1*. *Hum Mol Genet* 1997;6:1907-1915.
4. Kosaki K, et al. *Am J Hum Genet* 2000;66:309-312.
5. Blagitko N, et al. *Hum Mol Genet* 1999;8:2387-2396.

Editor's comment: Imprinted genes seem to lie in regions where there are both maternally and paternally imprinted genes. As the Human Genome Project proceeds, we should be able to identify all genes in a given region. It does seem that many regions are very complex and that each may be under different types of control. Clearly, chromosome 7 has something very important to do with growth and behavior since either deficiency of paternal expression or the duplication of maternal genetic material can lead to important changes in growth and behavior. Other forms of growth retardation very possibly are attributable to the imprinting phenomenon.

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