

acid 78 and the insertion of 4 extra amino acids from the first 12 bases of intron 2 into the 3' end of exon 2 (intron inclusion). Either aberration within the extracellular domain is expected to lead to abnormalities of ligand binding and hence hormone action.

Imbeaud S, et al. *Nature Genet* 1995;11:382-388.

Editor's comment: *MIS is a member of the transforming growth factor-6 (TGF-6) family. The MIS gene (chromosome 19p13.3) contains 5 exons and encodes a protein of 560 amino acids (including a leader sequence of 24 amino acids).¹ It is active as a disulfide-linked homodimer. PMDS has been associated with both normal and subnormal or absent production of AMH. In the latter group, abnormalities in the MIS gene have been detected, including deletions, nonsense mutations associated with stop codons, frameshift mutations leading*

to downstream stop codons, point mutations leading to instability of the protein molecule, and intronic splice donor point mutations.^{1,2} The majority of abnormalities have been found in exons 1 through 3. Identification of the receptor for MIS and documentation of its abnormality in a patient with PMDS provide further evidence of the importance of these proteins in male sexual differentiation. MIS is also produced by granulosa cells and is involved in the regulation of ovarian function. In the article by Imbeaud et al, PMDS results not from a mutated gene for MIS but a gene for its receptor. Again, the same apparent syndrome may be the same syndrome but of different gene origin.

Allen W. Root, MD

1. Josso N, et al. *Rec Prog Horm Res* 1993;48:1-59.
2. Imbeaud S, et al. *Hum Mol Genet* 1994;3:125-131.

No Reduction in Birth Weight in Phenylketonuria

A registry of all known children with phenylketonuria (PKU) born in the United Kingdom from 1964 onward allows the definition of growth parameters and natural history. The birth weight, sex, social class, gestational age, disease severity, and birth date were all taken into consideration when determining norms and averages. Data were available for 1,886 infants. The mean birth weight for PKU infants born in the United Kingdom was 3,306.7 g and the median 3,337 g. There are no significant differences from other births in the United Kingdom and PKU individuals show a similar pattern to the normal population.

Tillotson SL, et al. *Eur J Pediatr* 1995;154:847-849.

Editor's comment: *It is nice to have a proper natural history study that facilitates assessment of the natural history of a disorder. This PKU data gave completely normal growth findings in the affected newborn. This work is important since there has been a recent report suggesting impairment was already present at birth.*

Judith G. Hall, MD

A Gene (PEX) With Homologies to Endopeptidases Is Mutated in Patients With X-Linked Hypophosphatemic Rickets

The gene for familial X-linked hypophosphatemic rickets (FHR) has been localized to chromosome Xp22.1. By positional cloning, the present investigators have detected 4 partial deletions and 3 mutations (from a total of 150 families studied) in a gene in this region that is homologous to several endopeptidases such as neutral endopeptidase, endothelin-converting enzyme-1, and the Kell antigen. The deletions ranged in size from <1 to 55 kb; the mutations included loss of a dinucleotide, resulting in a frameshift, and 2 point mutations leading to exon skipping. This gene has been termed *PEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome). As do other members of the neutral endopeptidase family, *PEX* has many small exons, a short cytoplasmic amino-terminal domain, a transmembrane segment, and a large extracellular carboxyl-terminal region with a zinc-binding motif and 7 conserved cysteine residues. The investigators hypothesize that the *PEX* endopeptidase is important for processing a circulating factor that regulates function of the sodium-phosphate cotransporter (whose gene is situated on

chromosome 5q13). Loss of this endopeptidase would result in an inactive phosphate regulatory factor and decreased renal phosphate resorption.

The HYP Consortium. *Nature Genet* 1995;11:130-136.

Editor's comment: *Identification of a defective gene coding for an endopeptidase as the candidate gene for FHR leads to additional questions. For example, what is the target protein for PEX endopeptidase action and where is its gene located? How does this protein affect activity of the sodium-phosphate cotransporter? In addition, it introduces the probability that there are abnormalities in this and other factors that also lead to hyperphosphaturia, hypophosphatemia, and metabolic bone disease. Indeed, autosomal recessive and autosomal dominant forms of hypophosphatemic rickets and hypophosphatemic bone disease have been described that may involve these other proteins.*

Allen W. Root, MD