Editorial

Of Mouse and Man: The Hypophosphataemic Genes

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X-linked hypophosphataemia is the most frequent cause of familial rickets resistant to treatment with physiological amounts of vitamin D [1-3]. It is also one of the great mysteries of metabolic bone disease, since so little is known about phosphate regulation. However in the past decade research on phosphate transport in this disorder has been considerably illuminated by studies on the hypophosphataemic animal homologue, the Hyp mouse, whose mutant locus is at the distal end of the X chromosome [4]. Since not all physicians hold the mouse in high regard the clinical relevance of this work may have been undervalued; but recent discoveries now bring hypophosphataemic man and mouse together and provide a fascinating metabolic story. Not only has the human X-linked hypophosphataemic gene been localized [5-7] but another murine hypophosphataemic gene (called Gy) has been described, in which both hearing and the vestibular apparatus are defective [8].

What is the significance of these findings? What further lessons can be learnt from the mouse? And where should we go from here?

Inherited hypophosphataemia, and the rickets it usually causes, differs from all other forms of rickets, from acquired hypophosphataemia (often associated with specific tumours [9]), and also from phosphate depletion, as with excessive oral aluminium hydroxide [10]. Growth failure, widespread calcification of the tendons and ligaments [2, 11] which may lead to spinal stenosis and paraplegia [12] and absence of proximal myopathy, possibly related to normal intramyofibrillar inorganic phosphate concentration [13], distinguish X-linked hypophosphataemia. Although in this disease disturbances of parathyroid hormone and vitamin D metabolism have been sought, and sometimes found [14], this experiment of Nature certainly appears to be a primary disorder of phosphate transport and as such has the potential to teach us a lot about phosphate metabolism.

Important steps have been taken to identify the gene causing X-linked hypophosphataemia using the techniques of modern molecular biology. Multilocus linkage analysis was performed using a series of cloned X-chromosome genetic markers in 16 informative hypophosphataemic families from Britain, Canada and America [5, 7, 15]. These families had at least three generations in whom individuals were affected in a pattern consistent with X-linked dominant inheritance. The mutant locus was mapped to the short arm of the human X chromosome and its position could be related to the Hyp locus in the mouse by a scheme involving rearrangement of homologous blocks of genes [5]. This was the first dominant disease gene to be mapped to the...
human X chromosome. Although the closest markers are still some distance from the mutant locus they are potentially useful for prenatal diagnosis as they bridge the disease locus [7]. Furthermore since significant hypophosphataemia is difficult to be certain of in the neonatal period, a marker for the mutation could be very useful at this time both for prognosis and treatment [16].

So far the mutations in the human and mouse \( (\text{Hyp}) \) disorders appear identical. Where, then, does the other murine hypophosphataemic locus fit in? This is closely linked and distal to the \( \text{Hyp} \) locus with an apparently identical renal transport defect for phosphate. Oddly the male mutant mouse goes in circles (the female less so) and is therefore referred to as the \( \text{gyro} \) (gyrating) mouse and the mutant gene as the \( \text{Gy} \) gene [8]. The disorder of movement demonstrates that the \( \text{Gy} \) translation product is expressed in the inner ear as well as the kidney tubular cells. Pathologically the inner ear of the \( \text{Gy}/Y \) mouse is abnormal; the acoustic ganglion is deficient in cell bodies, the hair cells are degenerate, and the tectorial membrane is detached. The vestibular organs are also affected.

Although the phenotype of the \( \text{gyro} \) mouse does not have a recognized human equivalent, it is of considerable interest that a proportion of adults with inherited hypophosphataemia [17, 18] have sensorineural deafness, tinnitus and vertigo; whether this results from bony overgrowth or calcification of the ligaments in the inner ear or whether it is an independently inherited feature is unknown [8].

For the future there is no shortage of questions. We need more informative hypophosphataemic families and more genetic markers to get closer to the hypophosphataemic locus. We also need to look more closely at the clinical features of the human hypophosphataemic syndrome for evidence of linkage to other phenotypes. In this respect the astute physician could make an important contribution by spotting a patient with two major inherited diseases, one of which is hypophosphataemia. Such a patient would probably have an X-chromosomal deletion or translocation. Finding such a deletion would help to isolate the gene from a DNA library. Once the phosphate-regulating gene is identified its protein expression product can also be characterized. This will make it possible to advance our understanding of phosphate metabolism. Whatever direction future research takes we clearly cannot afford to neglect any lessons from the hypophosphataemic mouse.

REFERENCES