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Single base pair alterations as the predominant category of mutation in type I osteogenesis imperfecta

SIR,

The molecular pathology of type I osteogenesis imperfecta (OI) is beginning to be understood. Genetic linkage studies in a number of families have shown the type I collagen gene (*COL1A1*) to be the usual site of mutation in this dominantly inherited disorder.¹ A deficiency in the level of *COL1A1* mRNA or pro α 1(I) collagen is also frequently observed.^{2,3} In a limited number of subjects a pro α 1(I) collagen defect has been defined and for some of these cases the genetic lesion is also known.⁴ The DNA mutations include single base pair alterations as well as large deletion and insertion defects. However, because these cases were all initially identified as protein defects the observed DNA abnormalities do not necessarily represent the true spectrum of type I OI mutations. The present challenge in extending our understanding of this disorder is therefore to overcome the technical difficulties involved in studying the frequently encountered cases in which no protein defect is apparent or a *COL1A1* null allele exists.

In an attempt to meet this challenge we directly examined the *COL1A1* gene in genomic DNA samples from a series of nine independent type I OI patients. For five of these subjects previous linkage studies had shown *COL1A1* to be the defective loci¹ (data not shown). In the other four cases a *COL1A1* null allele had been indicated by protein and RNA studies (P Byers, 1988, personal communication).

The technique used for this study involved the S1 nuclease directed cleavage of heteroduplex DNA molecules formed between genomic material and cloned sequences. This approach to genomic DNA analysis was first described by Chebloune *et al.*⁵ The methodology used for our study (a modified version of that described in the initial report) was known to permit the detection of short length variations of the order of 4 bp in heterozygous subjects but not single base pair alterations.⁶

In all nine subjects the complete 18 kb *COL1A1* gene as well as 2 kb of 5' flanking sequence was examined as 11 contiguous domains of 1.4 to 2.5 kb. No mutation was found. A positive control, consisting of a 4 bp length mismatch, showed all experiments to be qualitatively successful.

These results indicate that in the nine cases examined, and hence probably in the majority of type I OI subjects, the genetic defect is likely to be a single base pair alteration. This being so it is necessary that the nature of all normal sequence variations in and around the *COL1A1* gene be determined so that small mutations such as these can be identified and the molecular pathology of type I OI more completely defined.

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Lethal osteogenesis imperfecta

SIR,

Two of us recently reported an infant with lethal osteogenesis imperfecta associated with a 46,XY,inv(7)(p13q22) karyotype in the *Journal of Medical Genetics*.¹ The parents are phenotypically normal; the mother has a 46,XX,inv(7)(p13q22) karyotype, and the father has a 46,XY karyotype. Because the gene for the pro α 2(I) chain of type I procollagen (*COL1A2*), a component of the principal collagen in bone, is assigned to the long arm of chromosome 7 at a site between bands q21 and q22,