A proband with lethal osteogenesis imperfecta has been investigated for the causative defect at the levels of collagen protein, mRNA, and DNA. Analysis of type I collagen synthesized by the proband’s fibroblasts showed excessive post-translational modification of α1(I) chain cDNA clones was used to locate an abnormality to exon 43 of the proband’s pro-α1(I) collagen gene (COL1A1). The nucleotide sequence of the corresponding gene region showed, in one allele, the deletion of 9 base pairs, not present in either parent, within a repeating sequence of exon 43. The mutation causes the loss of one of three consecutive Gly-Ala-Pro triplets at positions 868-876, but does not otherwise disrupt the Gly-X-Y sequence. Procollagen processing in fibroblast cultures and susceptibility of the mutant collagen I to cleavage with vertebrate collagenase were normal, indicating that the slippage of collagen chains by one Gly-X-Y triplet does not abolish amino-propeptide and collagenase cleavage sites. How the mutation produces the lethal osteogenesis imperfecta phenotype is not entirely clear; the data suggest that the interaction of α chains immediately prior to helix formation may be affected.

Osteogenesis imperfecta (OI) is a genetic disease characterized by fragility of bones. It is now well established that most, if not all, cases are the consequence of mutations in the genes coding for the pro-α1 and pro-α2 chains of type I collagen, the predominant protein in bone tissue (Byers, 1989, 1990; Prockop et al., 1989, 1990). Investigations at the protein and the nucleic acid levels have uncovered a number of different mutations, and a general picture has begun to emerge in which the type of mutation, the chain in which it occurs, and the position within that chain can be correlated with the severity of the clinical picture (Byers, 1989, 1990). The structural mutations most frequently identified in the collagen chains of patients with OI have been either substitutions of crucial glycine residues with other amino acids as a consequence of point mutations in the gene, sizeable deletions, insertions as a consequence of gene rearrangements, or other mutations leading to splicing defects ("exon skipping") and frameshifts (Byers et al., 1988; Byers, 1988; Cohn et al., 1986; Lamande et al., 1989; Tromp and Prockop, 1988; Willing et al., 1988, 1990). In this paper, we describe a hitherto unobserved mutation, i.e. a deletion of 9 base pairs in one of the COL1A1 alleles that causes the loss of a single Gly-X-Y triplet in half of the pro-α1(I) chains in cells from a baby with severe congenital OI (OI type IIA).

MATERIALS AND METHODS

The Patient—The proband (F. B., 20-4-1985) was born at term from healthy, unrelated parents. Birth weight, length, and head circumference were below the third centile for age. The clinical picture of severe congenital OI was immediately apparent because of short and deformed limbs; the baby died of respiratory insufficiency 3 h after birth. The radiological picture showed the classical, thick bone type of lethal OI (OI type IIA).

Cell Culture and Biochemical Studies—Skin fibroblasts were obtained from the patient, his parents, and normal controls with informed consent and were grown under standard conditions. Radiolabeled procollagens were obtained from cell cultures (passages 4-13) incubated with ascorbic acid, β-aminopropionitrile, [3H]proline, and [3H]glycine, as described (Steinmann et al., 1984). Triplet helical collagens were obtained by digestion of procollagens with papain as described (Steinmann et al., 1984). The thermal stability of papain-purified collagens was determined by trypsin or chymotrypsin digestion as described (Bruckner and Prockop, 1981; Superti-Furga et al., 1988a). Briefly, collagen preparations in 0.4 M NaCl, 0.1 M Tris-HCl, pH 7.4, were heated gradually to different temperatures, cooled quickly to 20 °C, digested for 2 min with either trypsin (1-tosyl-

amido-2-phenylethyl chloromethyl ketone-treated, Worthington; 20 µg/ml), or chymotrypsin (Worthington; 200 µg/ml), immediately frozen, and lyophilized. The lyophilisates were redisolved in hot sample buffer and analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Cleavage of papain-purified collagens with vertebrate collagenase (a generous gift from Dr. B. Adelmann, Max Planck, Munich) was performed in 50 mM Tris-HCl, 10 mM CaCl2, and 2 mM phenylmethylsulfonyl fluoride, pH 7.4, at room temperature for 16 h. The different procollagen and collagen preparations were analyzed by SDS-PAGE using the buffer system of Laemmli (1970) with 0.5 M urea (Steinmann et al., 1984). Two-dimensional mapping of cyanogen bromide peptides of collagen chains was performed as described (Steinmann et al., 1984), using a cleavage time of 90 min. After electrophoresis, the radiolabeled collagens were visualized by autoradiography (Laskey and Mills, 1975).
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RESULTS

Structure of the Collagen Molecules Produced by the Proband’s Fibroblasts—The proband’s cells produced a population of normal type I collagen chains and a population of α1(I) and α2(I) chains that migrated more slowly on SDS-PAGE. When cultures were labeled at 30 rather than at 37 °C to reduce the thermodynamic stress on the helix, only normally migrating chains were observed (Fig. 1a), indicating that the reduced mobility was caused by excessive post-translational modification rather than by a peptidyl insertion (Suortti-Furga et al., 1988b). Two-dimensional cyanogen bromide mapping of α chains showed that there was marked overmodification of all cyanogen bromide fragments, indicating a structural defect in the carboxy-terminal region of the triple helix or in the C-propeptide. When procollagen preparations were analyzed by electrophoresis without prior digestion with pepsin, the amount of partially and fully processed chains, i.e. pN, pC, and mature α1(I) and α2(I), was similar to that of control preparations, indicating that cleavage of the C- and N-propeptides was not substantially impaired by the structural mutation in the molecule.

The population of overmodified type I collagen molecules had the same thermal denaturation behavior as its normal counterpart (Tm = 41.5 °C) (not shown). After a 16-h incubation with vertebrate collagenase, both the normal and the overmodified type I collagens were completely cleaved, giving rise to the fragments of typical size (Woolley, 1984) (not shown).

RNA A Mapping—Total RNA was prepared from flasks of confluent cells (Chomczynski and Sacchi, 1987).

Antisense 32P-labeled transcripts were generated from overlapping cDNA fragments, derived from the human pro-α1(Ⅰ) collagen cDNA clones Hf404 and Hf677, subcloned into the transcription vectors pTZ18R and pTZ19R (Mead et al., 1986).

In vitro transcription was carried out under the following conditions: 0.5 mM GTP; 0.5 mM ATP; 0.5 mM UTP; 7.5 μM CTP; 40 mM Tris-HCl, pH 8.25; 6 mM MgCl2; 2 mM spermidine HCl; 10 mM dithiothreitol; 0.2 mg/ml bovine serum albumin; 35 units RNasin (Promega Biotech); 10 units of T7 RNA polymerase (Pharmacia LKB Biotechnology, Inc.); 40 μCi of [32P]CTP (800 Ci/mmole; Amerham Corp.); 0.25 μg of linearized template DNA in a volume of 10 μl for 2 h at 37 °C. 6 units of DNase I (RNase-free) (Pharmacia) was then added and incubated for a further 15 min at 37 °C. The reaction mix was then phenol-extracted, ethanol-precipitated, and resuspended in 20 μl of distilled water. 1-μl probe was mixed with 50 μg of total cellular RNA, ethanol-precipitated, and resuspended in 200 μl of 80% formamide, 400 mM NaCl, 40 mM PIPES, pH 6.7, heated to 85 °C for 5 min, and hybridized overnight at 60 °C.

The RNA-RNA hybrids were enriched by mRNA purification by Hybond-mAP chromatography (Amersham) and then digested with RNase A (Gibbs and Caskey, 1987). Subsequent analysis of RNase A-protected transcripts was as described (Winter et al., 1986).

Amplification, Cloning, and DNA Sequencing—DNA was isolated from confluent fibroblasts using a procedure involving treatment with sodium dodecyl sulfate, digestion with proteinase K, and phenol extraction (Maniatis et al., 1982).

Polymerase chain reaction amplifications were carried out in 50-μl reactions containing 1 μg of genomic DNA and 1.4 units of Taq DNA polymerase (Anglian Biotech) according to the manufacturer’s directions. 30 cycles each of 1.5 min at 95 °C, 1.5 min at 60 °C, and 5.5 min at 70 °C were performed by a programmable Dri-Block PHC-1 (Techne, Cambridge, United Kingdom). The amplified fragment was digested with NarI and cloned into Clal-digested pBluescript SK- (Stratagene) (Snort et al., 1988). Plasmid DNA sequence determination was by the chain termination method using T7 DNA polymerase (Tabor and Richardson, 1987) from “mini-prep” DNA samples (Kraft et al., 1988).

Mutation Inheritance Analysis—1-μg samples of genomic DNA were amplified for 30 cycles as described above, phenol-extracted, ethanol-precipitated, and resuspended in 20 μl of distilled water. 1-μl aliquots were digested and electrophoresed on a 12% polyacrylamide gel.

Since the mismatch could lie in one of two orientations with respect to the BX887 probe, two new subclones were constructed covering the helical and carboxyl-telopeptide regions of the pro-α1(Ⅰ) cDNA clones Hf404 and Hf677. These were used to generate antisense RNA probes for a study of mapping mutations in cases of perinatal lethal osteogenesis imperfecta. One subclone BX887 (Fig. 2a) when used as a probe in RNase A mapping experiments with RNA from the proband described here gave, in addition to the 871-base-long fully protected fragment, two cleavage products of approximately 545 and 335 bases (Fig. 2b, lanes A), indicating a mismatch between the probe and the target RNA.

FIG. 1. Gel electrophoresis of pepsin-treated collagen produced by the patient’s fibroblasts. Cells were radiolabeled at 37 and 30 °C, the medium was treated with pepsin, and the collagens electrophoresed in the first dimension on a 5% gel (horizontal lanes). Two-dimensional cyanogen bromide mapping of collagen secreted at 37 °C was done as described under “Materials and Methods” on a 70% gel (lower panel). Note that at 30 °C, the doublets of the α1(I) and α2(I) chains disappear, while at 37 °C, the whole collagen molecule is overmodified as indicated by the diagonal shape of the spots.

RNase A Mapping of a Mutation in the Pro-α1(I) Gene—Five overlapping subclones were constructed covering the helical and carboxyl-telopeptide regions of the pro-α1(I) cDNA clones Hf404 and Hf677. These were used to generate antisense RNA probes for a study of mapping mutations in cases of perinatal lethal osteogenesis imperfecta. One subclone BX887 (Fig. 2a) when used as a probe in RNase A mapping experiments with RNA from the proband described here gave, in addition to the 871-base-long fully protected fragment, two cleavage products of approximately 545 and 335 bases (Fig. 2b, lanes A), indicating a mismatch between the probe and the target RNA.

Cloning and Sequencing the Region of the Mutation—To characterize the mutation, genomic DNA was prepared from the proband’s fibroblasts. An 850-base pair fragment containing the mutated region was amplified by the polymerase chain reaction (PCR) (Fig. 3a). The amplified DNA was digested
collagen molecules, sometimes preventable by incubation at low temperature, is a typical finding in patients with OI, especially its lethal variants (Steinmann et al., 1984; Bonadio and Byers, 1985; Byers, 1989), and points to a structural defect within the triple helical domain (Superti-Furga et al., 1988b; Royce and Steinmann, 1988). The finding of a normal thermal stability, however, was apparently at odds with the notion of a defect within the triple helical part of the molecule. Thus, this patient was an interesting candidate for a search of the mutation at the mRNA and DNA level using the RNA:RNA hybrid RNase A cleavage technique.

RNase A cleavage mapping (Winter et al., 1985; Myers et al., 1985; Gibbs and Caskey, 1987) is a technique capable of detecting point mutations and is particularly useful in the study of OI mutations as analysis can be restricted to coding regions of the gene, and the relevant RNAs are abundant. The technique may be capable of detecting up to 50% of point mutations, the degree of cleavage being dependent upon not only the specific mismatch, but also the flanking sequences (Winter et al., 1985; Lopez-Galindez et al., 1988). Being unable to detect all point mutations, the technique will tend to favor the detection of deletions and insertions, however small. We

**FIG. 3. Characterization of the COL1A1 mutation.** a, genomic amplification strategy. The boxed regions represent exons whose sizes are indicated below in base pairs. The two NarI sites used to clone segments of the amplified DNA are marked, as is the Sau3AI site corresponding to the 3' end of probe RS355. The vertical arrow indicates the approximate position of the mutation. The position of the PCR primers is marked above the gene. The left-hand primer (L) has the sequence 5' CGGAACTCCCTGCCGCCC TGTCTCA 3', and the right-hand primer (R) has the sequence 5' CGGCCTGTCCCGCC TGTCTCA 3'. The amplified fragment was approximately 850 base pairs in size. b, DNA and corresponding amino acid sequence of the mutant and wild-type alleles of the proband. Amino acid residues 865 and 877 of α1(I) procollagen are marked. Boxed regions indicate the repeating DNA motif, which is imperfect in the final repeat.

**DISCUSSION**

The initial biochemical analysis of the type I collagen synthesized by cultured fibroblasts of this newborn with lethal osteogenesis imperfecta showed excessive post-translational modification after incubation at 37 °C, lack of overmodification after incubation of the cells at 30 °C, and a normal thermal stability of the triple helical portion of the overmodified molecules as determined by gradual heating and proteolytic digestion. Excessive overmodification of type I collagen molecules, sometimes preventable by incubation at low temperature, is a typical finding in patients with OI, especially its lethal variants (Steinmann et al., 1984; Bonadio and Byers, 1985; Byers, 1989), and points to a structural defect within the triple helical domain (Superti-Furga et al., 1988b; Royce and Steinmann, 1988). The finding of a normal thermal stability, however, was apparently at odds with the notion of a defect within the triple helical part of the molecule. Thus, this patient was an interesting candidate for a search of the mutation at the mRNA and DNA level using the RNA:RNA hybrid RNase A cleavage technique.

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**FIG. 4. Analysis of mutation inheritance.** Ethidium bromide-stained 12% acrylamide gel is shown. DNA was amplified as described in the text and digested with BstEII and Mbol. The lanes are as follows. 1 and 2, control DNAs; 3, the proband's father; 4, the proband; 5, the proband's mother. Sizes are marked in base pairs.
used RNase A cleavage to map a mutation to exon 45 of COL1A1 in a patient with sporadic lethal OI. DNA sequencing revealed the mutation to be a 9-base pair deletion from one allele. The region from which the 9 base pairs were lost is of a repetitive nature and consists, in the normal gene, of two full repeats of 9 base pairs and one near repeat of 8 base pairs.

In the light of the sequence data, we can speculate as to the cause of the heterogeneous cleavage products obtained with probe RS355. In the formation of the heteroduplex of the probe and the mutant RNA a "bubble" may be formed with three repeats on the probe strand and two repeats on the mRNA strand. Three conformations of interaction between the strands are possible, each involving loops in the probe strand. If the bubble "zips up" from one end of the repetitive region, a loop at the end of the repetitive region will be formed producing either the upper or the lower doublet band depending on the direction of the zipping up. If the bubble zipped up from each end simultaneously, the middle repeat would loop out and the middle doublet band be seen on the gel. From the intensity of the middle doublet, it would appear that the simultaneous bidirectional zipping up is the preferred event. The presence of each product as a doublet may represent partial cleavage of the loop by RNase A, or nibbling from the ends of the heteroduplex.

As the deletion arose in a repetitive region, it is not possible to precisely define the mutation, there being 18 possible "windows" for the deletion in the 26-base pair repetitive region. The deletion boundaries could have occurred within codons without the possibility of producing an amino acid substitution as a result of the deletion. Thus, wherever the deletion occurred, the result would be the loss of one Gly-Ala-Pro unit.

The data clearly indicated that a new type of mutation, the loss of a single Gly-X-Y triplet, was present in half of the pro-α1(I) chains synthesized by the patient's fibroblasts. Coincidently, an almost identical mutation, i.e. a 9-base pair deletion in COL1A1 leading to the loss of the Gly-Ala-Pro triplet at position of 874–876 of the pro-α1(I) chain, has been reported, in preliminary form, for another baby with sporadic lethal OI (Wallis et al., 1989). A similar type of deletion has been observed in a case of pyruvate dehydrogenase deficiency (Dahl et al., 1990) where one copy of a 9-base pair direct repeat was deleted, resulting in a frame shift. It has been suggested that direct repeat sequences, especially those that are GC-rich, are often involved in DNA rearrangements (Chandley, 1989).

Although there is little doubt about the fact that this mutation is indeed the cause of the OI phenotype, the mechanism by which the biochemical and clinical phenotype are produced is not clear. It is therefore appropriate to compare the effects of this mutation to those of other mutations observed so far, i.e. point mutations or larger deletions. Glycine substitutions within the triple helical region usually (but not always) cause enough distortion of the helix to result in a decreased stability of the molecule (Steinmann et al., 1984; de Vries and de Wet, 1986; Constantinou et al., 1989). Deletions of one or more exons also have marked effects on the stability of the molecule, apparently by disrupting specific interactions between adjacent residues on different chains. The normal thermal stability of mutant type I collagen produced by this patient's cells is consistent with the fact that the mutation does not disrupt the Gly-X-Y sequence and thus does not introduce any distortion in the helical structure.

The finding of increased post-translational modification, on the other hand, implies a delay in formation of a triple helix. The reason for such a delay is not clear, since, unlike in other cases of lethal OI, the mutation does not disrupt the Gly-X-Y pattern and should not interfere with the propagation of the helical conformation from the carboxyl terminus toward the amino terminus of the molecule. The current model of procollagen helix formation involves a direct transition from a random coil to a triple helical configuration; this model may be too simple insofar as interactions between α chains amino-terminal to the already entwined triple helix may be necessary to facilitate helix formation. In other words, the still unhelical α chains may not be as free of interchain relations as has been so far believed, there being an intermediate state of loose association ("chain registration") that precedes the final triple helical configuration. Experimental data in favor of such an intermediate level of structure have recently been presented (Veis and Kirk, 1989). It is conceivable that the mutation in this patient interferes with this particular state of association, thereby delaying the formation of the helix, but without affecting the stability of the triple helix once it is formed.

The mutant type I collagen molecules were apparently susceptible to cleavage both with vertebrate collagenase (in vitro) and with aminopeptidase (in culture) in spite of the partial misalignment that must have been present in molecules containing the shortened chains. Apparently, a slight shift of one chain relative to the other does not significantly change the conformation of the collagenase and aminopeptidase cleavage sites. However, we did not perform detailed kinetic studies, which might well have uncovered some form of partial resistance (Vogel et al., 1988).

In conclusion, the available biochemical data suggest that deletion of a single Gly-Ala-Pro triplet in the CB6 region of the pro-α1(I) chains is capable of producing the phenotype of lethal osteogenesis imperfecta by delaying formation of the triple helix of type I collagen and causing increased post-translational overmodification without affecting the subsequent stability of the helix. The exact mechanism by which helix formation is disturbed remains unclear, although it may involve the interaction of pro-α chains prior to the formation of the triple helix. The findings imply that our current view of chain assembly and triple helix formation may have to be modified to include a phase of interaction between pro-α chains (chain registration) preceding the final helical configuration.

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