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Gene Section
Review

COL1A1 (collagen, type I, alpha 1)

Marie-Pierre Simon, Georges Maire, Florence Pedeutour

Institute of Signalling, Developmental Biology and Cancer Research, CNRS UMR 6543, Centre Antoine-Lacassagne, 06189 Nice cedex 2, France (MPS); UF Recherche Clinique 952, Laboratoire de Génétique, Université de Nice-Sophia Antipolis, CHU de Nice, 06202 Nice, France (GM, FP)

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Identity

HGNC (Hugo): COL1A1

Location: 17q21.31-q22

Local order: Telomeric to MEOX1 (mesenchyme homeo box 1), centromeric to MVWF (Modifier of von Willebrand factor).

COL1A1 (17q21) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

The COL1A1 gene is 18 kb in size and is composed of 52 exons. Exons 6 to 49 encode the alpha helical domain. Most of these exons were 45 bp, 54 bp or multiple of 45 bp or 54 bp.

Transcription

Two RNA of 5,8 kb and 4,8 kb differing by their 3' terminus non coding sequence and giving rise to a single 140 kDa protein.

Protein

Description

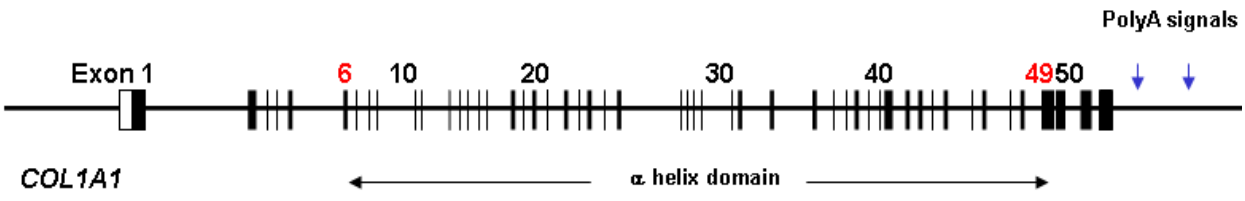
1464 amino acids. The a1 (I) chains of the type I collagen are synthesised as procollagen molecules containing amino and carboxy-terminal propeptides, wich are removed by site-specific endopeptidase. The central triple helical domain is formed by 338 repeats of a Gly-X-Y triplet where X and Y are often a proline.

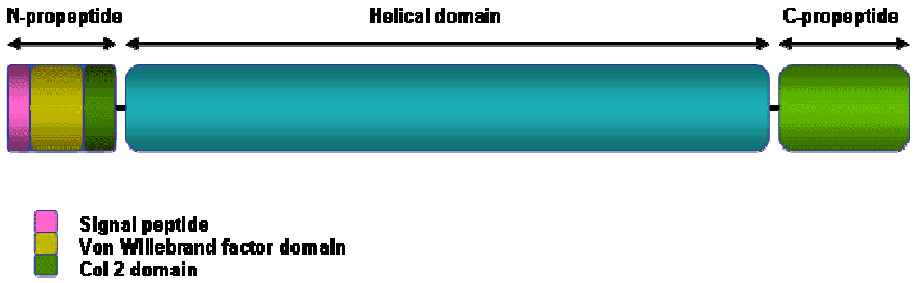
Expression

Type I collagen is the most abundant protein in vertebrates and a constituent of the extra cellular matrix in connective tissue of bone, skin, tendon, ligament and dentine. It is mostly produced and secreted by fibroblasts and osteoblasts.

Localisation

Extra-cellular matrix.





Function

Two pro a1 (I) chain associate in trimers with one pro a2 (I) chain to form the type I collagen fibrils after proteolysis.

Homology

Member of the collagen family.

Implicated in

Dermatofibrosarcoma Protuberans (DP)

Also called:

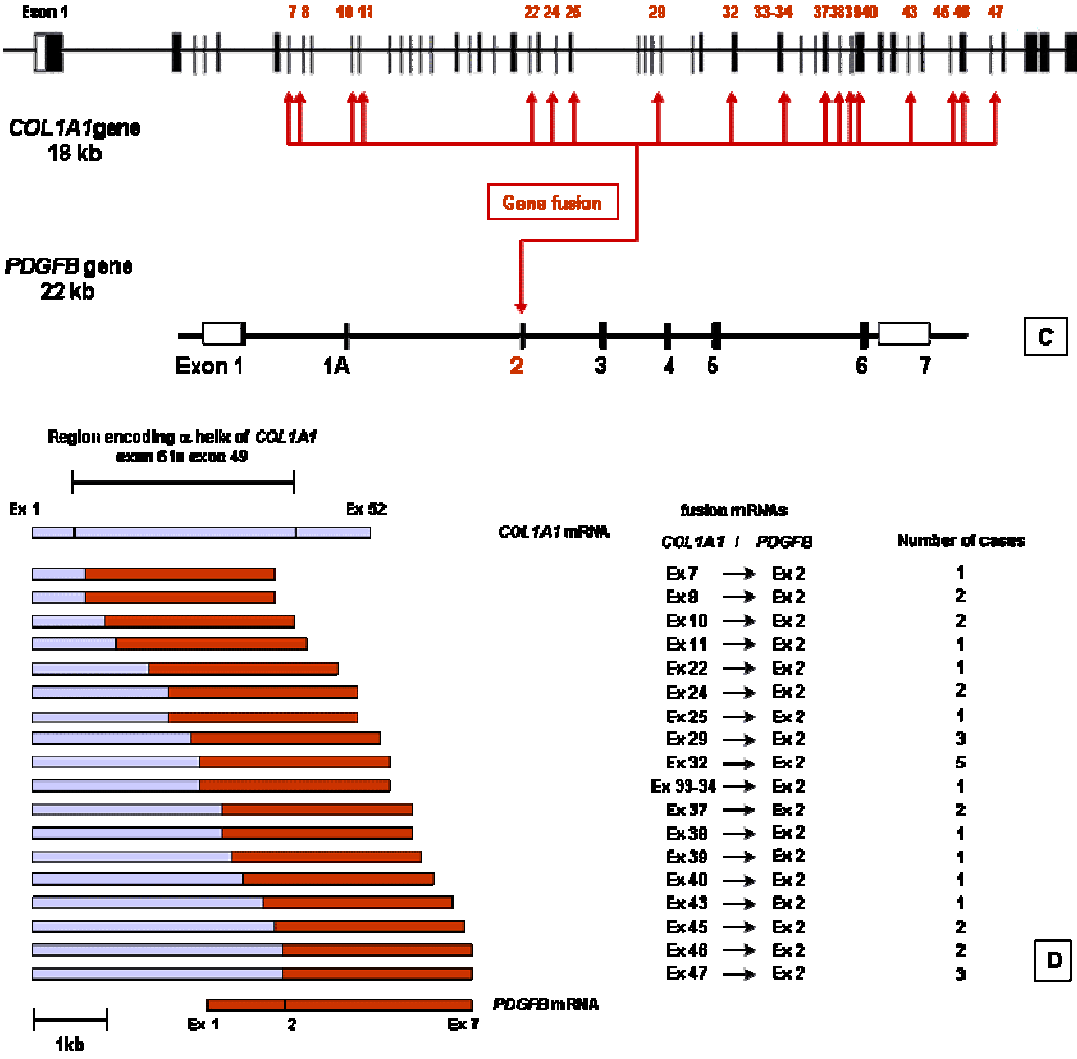
-Darier Ferrand tumour or Darier-Hoffmann tumour.
-Giant cell fibrosarcoma (GCF) (juvenile form of DP).
- Bednar tumour (pigmented variant of DP).

Disease

Infiltrative skin tumours of intermediate malignancy.

Prognosis

The prognosis is usually favourable. These tumours are locally aggressive and highly recurrent, but metastases or tumour-related deaths are extremely rare.



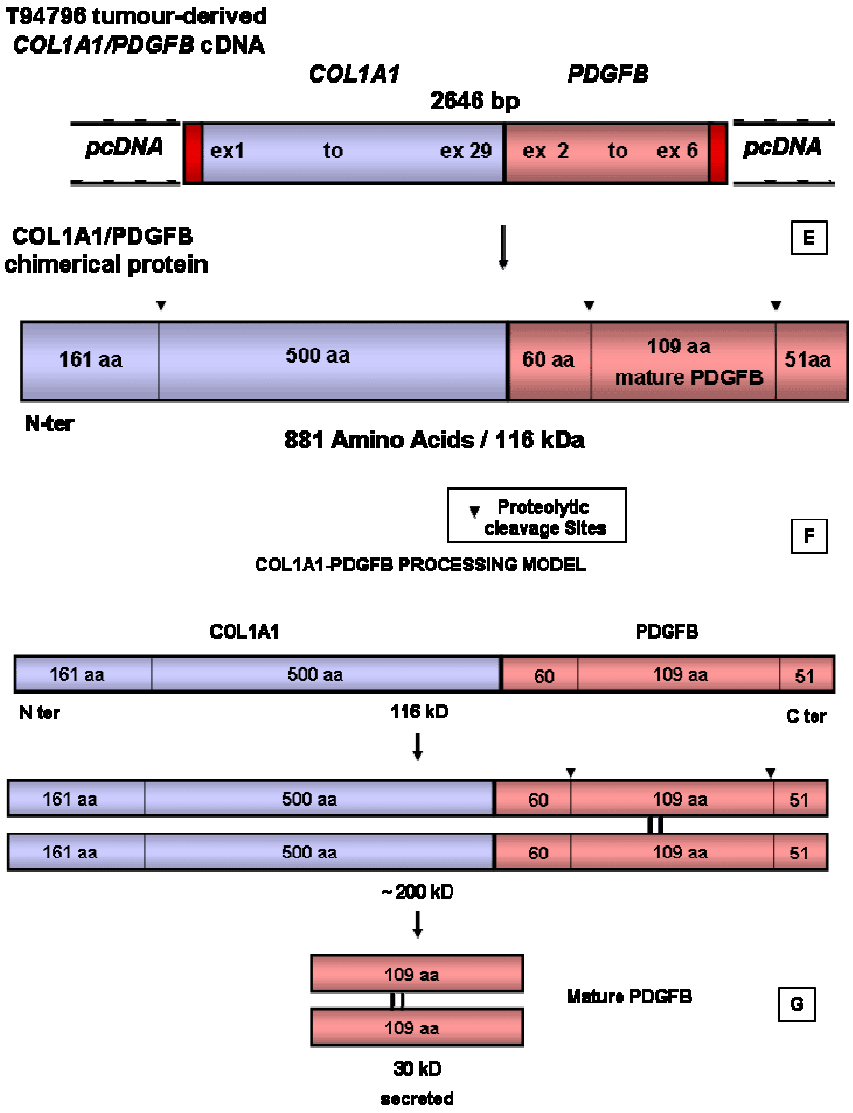
Cytogenetics

Dermatofibrosarcoma Protuberans, Giant Cell fibrosarcoma and Bednar tumours present specific cytogenetic features such as reciprocal translocations t(17;22)(q22;q13.1) (Fig A) or, more often, supernumerary ring chromosomes derived from t(17;22) (B). As shown by FISH analysis, the ring chromosomes contain chromosome 22 centromere and low-level amplification of 22cen-q13.1 and 17q22-qter sequences. To note, in most cases, the derivative chromosome 17 is not present. In contrast, several copies of the derivative chromosome 22 are generally observed.in addition to two apparently normal chromosomes 17.

Hybrid/Mutated gene

Both rings and der(22) translocated chromosomes present a same molecular rearrangement that fuses the collagen type I alpha 1(COL1A1) and the platelet-derived growth factor B chain (PDGFB) genes (C).

In all DP and GCF cases studied, the t(17;22)translocation results in chimerical COL1A1/PDGFB mRNA production, in which the PDGFB exon 1 is deleted and replaced by a variable segment of COL1A1 mRNA sequence. In the 32 cases tested the fusion mRNA was an in-frame fusion of one of the COL1A1 exons (varying from exon 7 to exon 47) to PDGFB exon 2 (D).



A chimerical COL1A1/PDGFB cDNA sequence fusing COL1A1 exon 29 to PDGFB exon 2 was isolated from the DP T94796 tumour and stably transfected in the Chinese hamster lung fibroblastic cell line PS200 (E). The T94796 COL1A1/PDGFB chimerical protein sequence retained the COL1A1 N-terminus processing site encoded by the COL1A1 exon 6 and the N and C-terminus PDGFB processing sites encoded by the PDGFB exons 3 and 6 respectively (F). Mutagenesis experiments and immunodetection with anti-PDGFBB and specific anti-COL1A1/PDGFB antibodies showed that COL1A1/PDGFB expressing cells produced 116 kD chimerical COL1A1/PDGFB precursors chains, which formed dimers and were processed to give active 30 kD PDGFB-like dimers (G).

Abnormal protein

COL1A1 and PDGFB are both encoded as pro-peptides, which are processed by proteolytic cleavage at N and C-terminus, to give mature proteins. Sequences analyses of the chimerical COL1A1/PDGFB fusion transcripts showed that the COL1A1/PDGFB putative proteins displayed a pro-peptide structure, which preserved the N-terminus COL1A1 pro-peptide containing the signal peptide and the N and C-terminus PDGFB maturation cleavage sites.

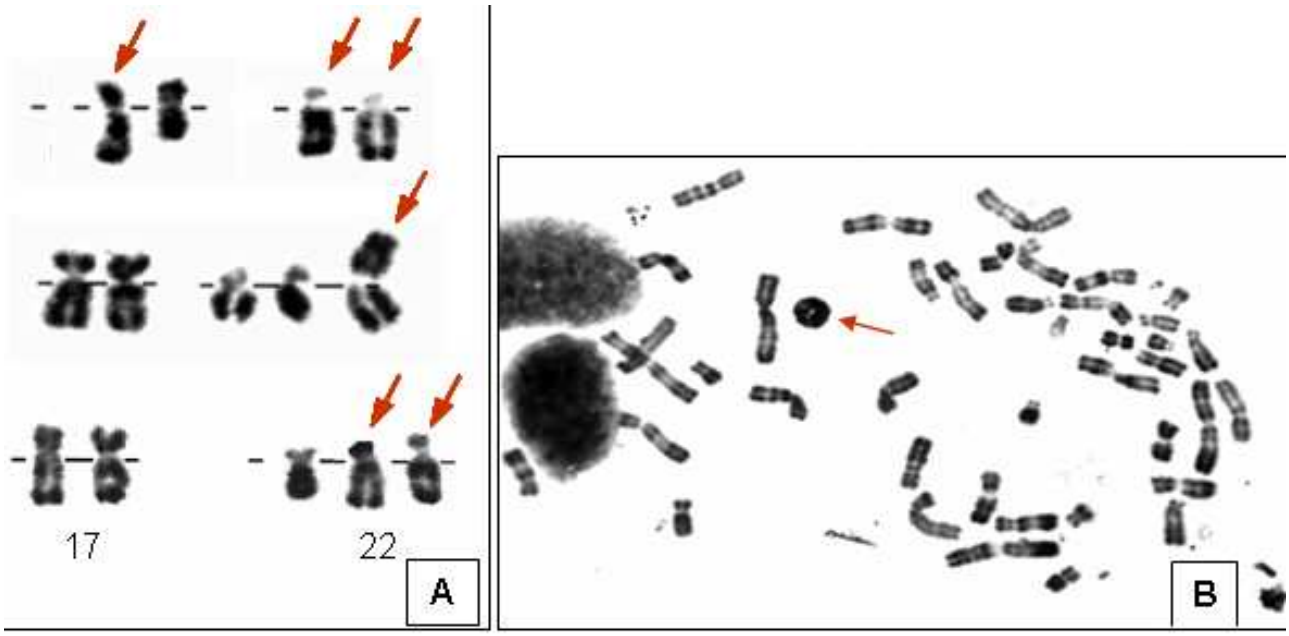
The functional and structural properties of the COL1A1/PDGFB fusion protein were characterized by generating stable fibroblastic cell lines that expressed tumour-derived COL1A1/PDGFB chimerical genes. The diagram herein given presents the COL1A1/PDGFB chimerical protein encoded by the T94796 tumour-derived chimerical COL1A1/PDGFB cDNA sequence.

Oncogenesis

Transfected cells lines expressing the chimerical T94796-COL1A1/PDGFB proteins became independent upon growth factors, including PDGFB, and induced tumours formation in nude mice. In addition, it was shown that the COL1A1/PDGFB stable clones cells contained activated PDGF b-receptors and that the conditioned media from COL1A1/PDGFB transfected cells were able to stimulate fibroblastic cells growth. Anti-PDGFBB antibodies neutralized this effect.

These results strongly suggest that the COL1A1/PDGFB chimerical gene expression associated with DP, contributes to tumour formation through ectopic production of mature PDGFB and the formation of an autocrine loop.

Breakpoints



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