Rôle de FAM20C dans la physiologie gingivale

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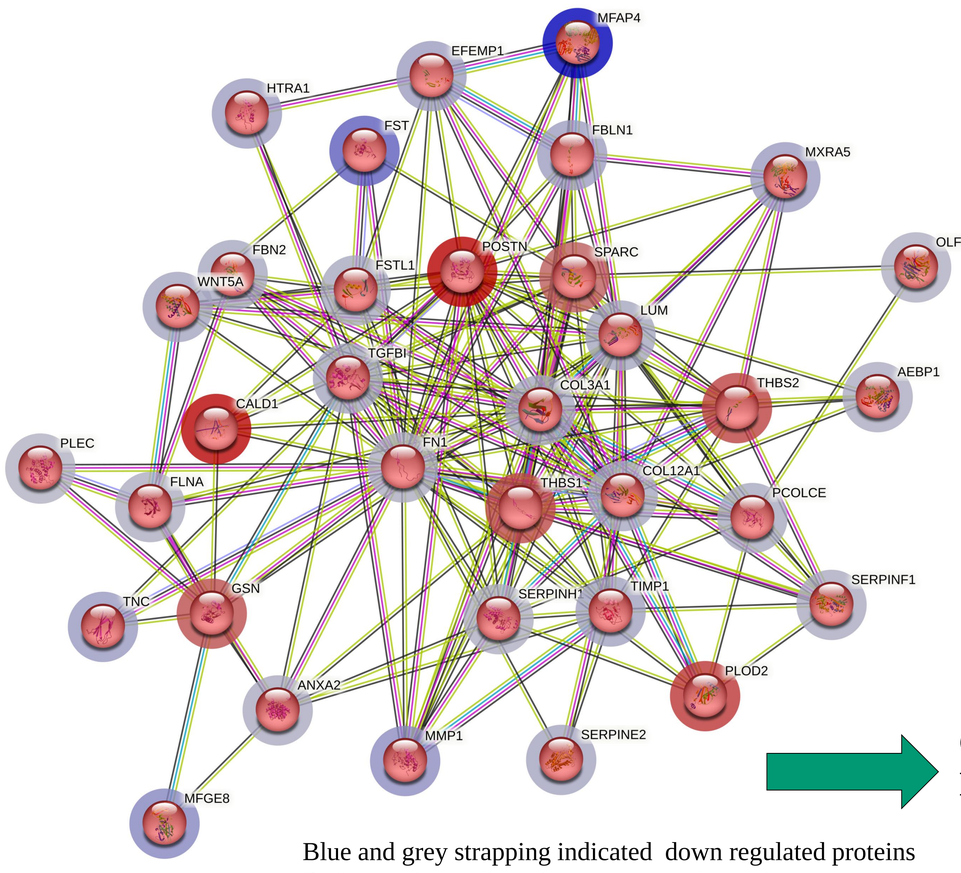
Abstract

Raine syndrome (RNS), or osteosclerotic bone dysplasia, is a rare disease characterized by craniofacial abnormalities, including gingival fibromatosis. RNS is caused by bi-allelic mutations in the gene encoding the atypical serine protein kinase FAM20C involved in the extracellular matrix protein secretion pathway. How FAM20C variants alter gingival connective tissue homeostasis is currently unknown. We analyzed by mass spectrometry the secretomes and cellular proteomes of normal gingival fibroblasts (GF) and RNS patients. We identified a set of 59 dysregulated proteins in the secretomes of RNS patients with 11 increased proteins and 48 decreased proteins as well as a set of 318 dysregulated proteins in the cellular proteomes with 24 increased proteins and 294 decreased proteins. This set defines two interconnected interactomes, one centered on fibrosis and the other on the organization of the cytoskeleton. For most overexpressed proteins, quantitative RT-PCR analysis showed increased transcription levels in vitro. We have confirmed in vivo on sections the increased expression of these targets such as Periostin or Collagen type I. Our preliminary studies indicate that FGs from RNS patients migrate more slowly than normal FGs in the scratch assay. Further analyzes are needed to show a different migratory behavior of GFs from RNS patients. In conclusion, our data strongly suggest that FAM20C variants alter the composition of the extracellular matrix by promoting the expression of pro-fibrotic markers and migratory/exploratory behavior via modulation of the actin cytoskeleton

Secretome of GFs mutants

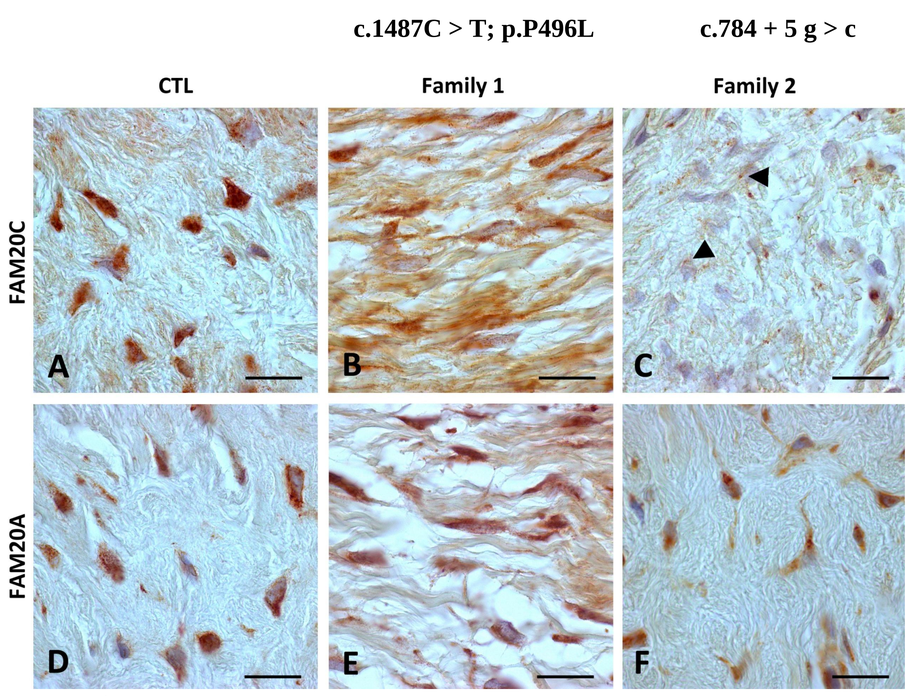


GO Process	Extracellular matrix organization
GO Process	Collagen fibril organization
GO Process	Regulation of transforming growth factor beta production
GO Process	Peptide cross-linking
GO Process	Positive regulation of transforming growth factor b1 production
GO Function	Extracellular matrix structural constituent
GO Function	Collagen binding
GO Function	Integrin binding
GO Function	Proteoglycan binding
GO Function	Peptidase regulator activity
GO Component	Extracellular matrix
GO Component	Collagen-containing extracellular matrix
GO Component	Basement membrane
GO Component	Platelet alpha granule
GO Component	Platelet alpha granule lumen
KEGG	ECM-receptor interaction
Reactome	Extracellular matrix organization

Blue and grey strapping indicated down regulated proteins
Red strapping indicated overexpressed proteins

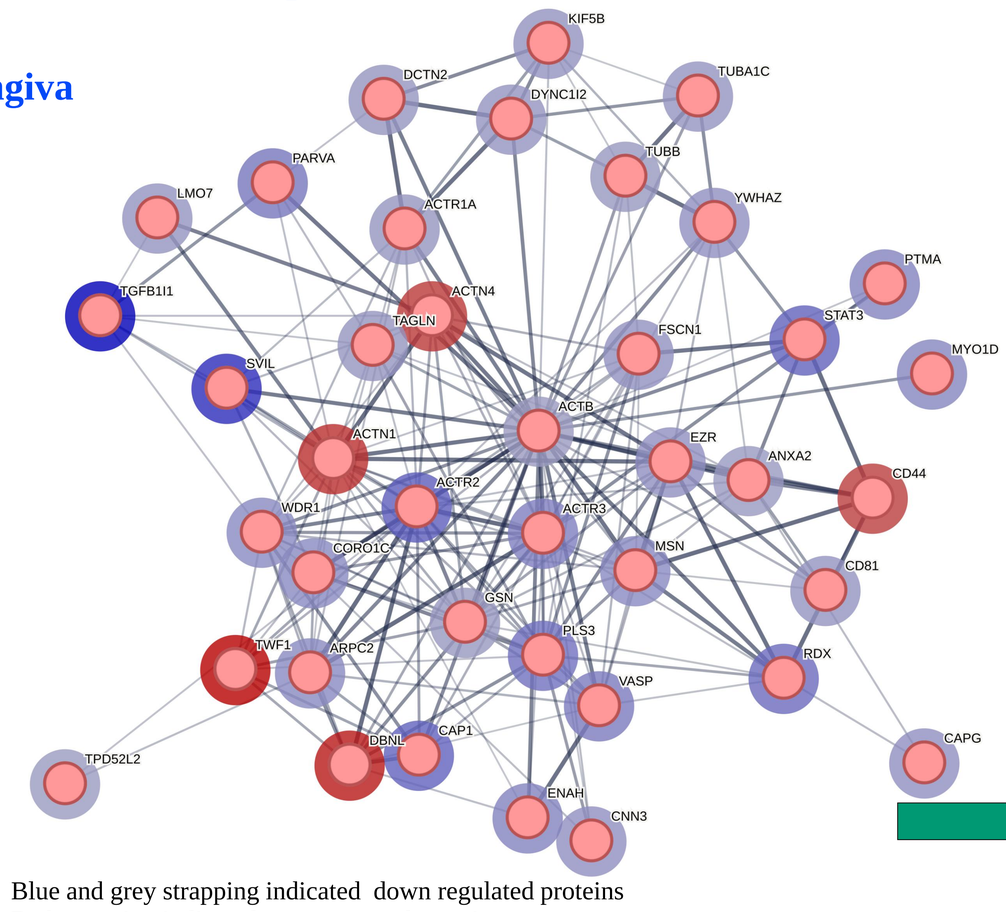
Changes in extracellular matrix
Increased stiffness, fibrotic behaviour

FAM20C and FAM20A expression in normal and RNS gingiva



FAM20C and FAM20A expression in fibroblasts

Cellular proteome of GFs mutants, main cluster

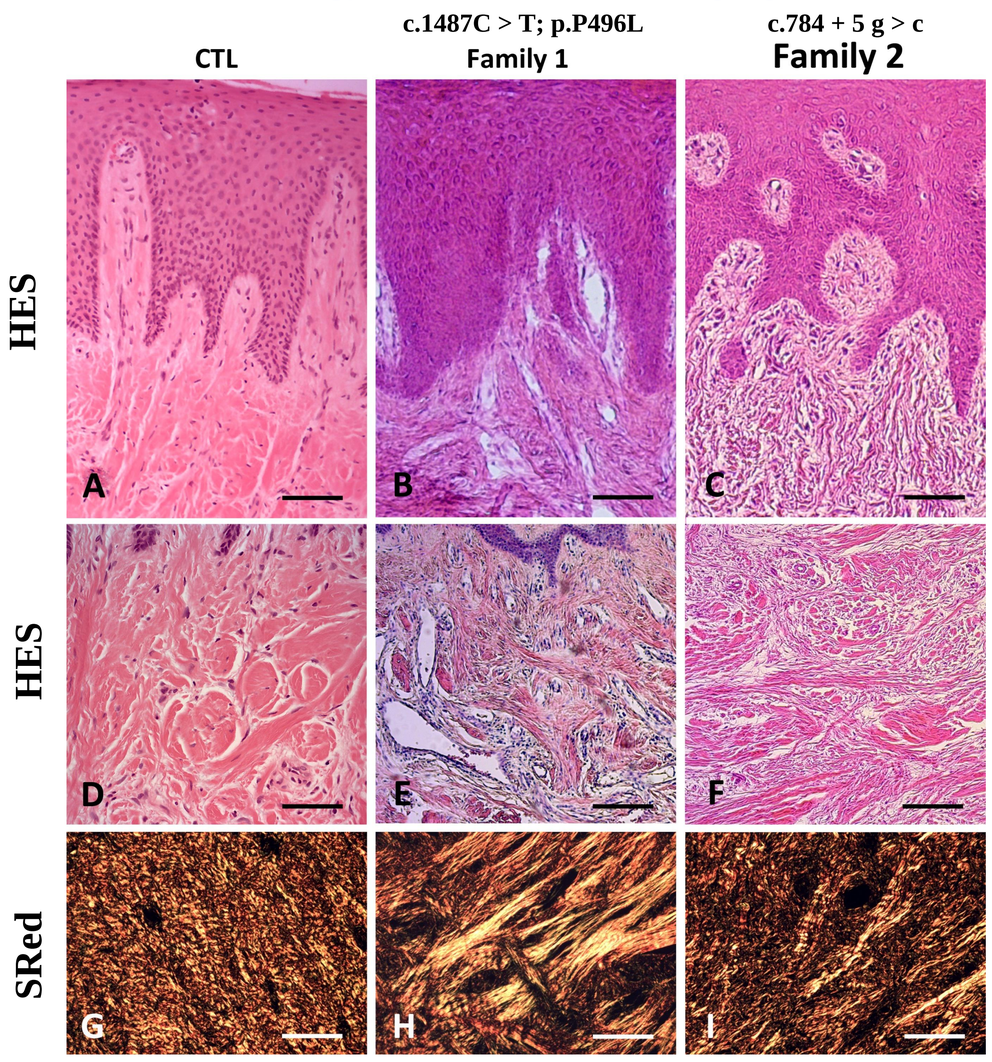


GO Process	Actin filament organization
GO Process	Actin polymerization or depolymerization
GO Process	Regulation of lamellipodium organization
GO Process	Positive regulation of lamellipodium organization
GO Process	Regulation of actin filament depolymerization
GO Function	Actin binding
GO Function	Actin filament binding
GO Function	Structural constituent of cytoskeleton
GO Function	phosphatidylinositol-4,5-bisphosphate binding
GO Function	Cytoskeletal protein binding
GO Component	Cytoskeletal protein binding
GO Component	Actin cytoskeleton
GO Component	Lamellipodium
GO Component	Invadopodium
GO Component	Cortical cytoskeleton
KEGG	Regulation of actin cytoskeleton
Reactome	Cell-extracellular matrix interactions

Blue and grey strapping indicated down regulated proteins
Red strapping indicated overexpressed proteins

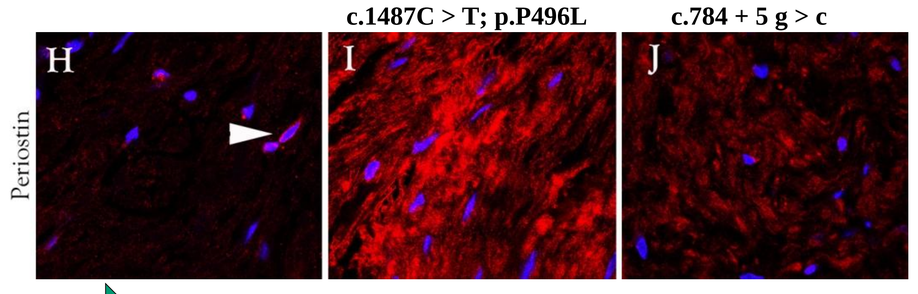
Changes in actin cytoskeleton

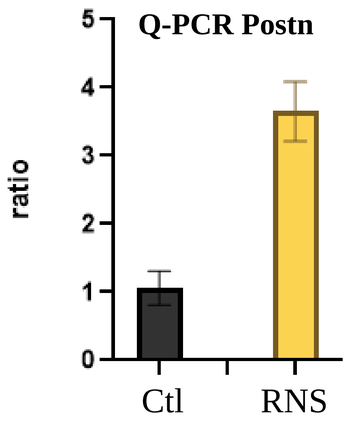
Histology of normal and RNS gingiva



Abnormal vascularization, firomatosis

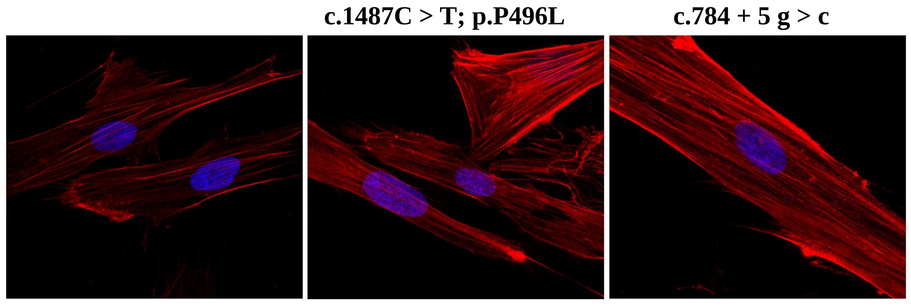
Periostin expression in vivo and in vitro





Increased Postn expression in vivo and in vitro in gingival tissues of of RNS patients

Actin cytoskeleton in vitro



Increased dorsal actin fibers in RNS patients

CONCLUSION: The diminution in FAM20C induces a major rearrangement of the extracellular matrix and the interaction between ECM-receptor-actin skeleton.