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# FOP & POH

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Attività di diagnostica per FOP iniziata nell'estate del 2006

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ARTICLE

# Mutational analysis of the *ACVR1* gene in Italian patients affected with fibrodysplasia ossificans progressiva: confirmations and advancements

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**Fibrodysplasia ossificans progressiva (FOP, MIM 135100) is a rare genetic disorder characterized by congenital great toe malformations and progressive heterotopic ossification transforming skeletal muscles and connective tissues to bone following a well-defined anatomic pattern of progression. Recently, FOP has been associated with a specific mutation of *ACVR1*, the gene coding for a bone morphogenetic protein type I receptor. The identification of *ACVR1* as the causative gene for FOP now allows the genetic screening of FOP patients to identify the frequency of the identified recurrent *ACVR1* mutation and to investigate genetic variability that may be associated with this severely debilitating disease. We report the screening for mutations in the *ACVR1* gene carried out in a cohort of 17 Italian patients. Fifteen of these displayed the previously described c.617G > A mutation, leading to the R206H substitution in the GS domain of the ACVR1 receptor. In two patients, we found a novel mutation c.774G > C, leading to the R258S substitution in the kinase domain of the ACVR1 receptor. In the three-dimensional model of protein structure, R258 maps in close proximity to the GS domain, a key regulator of ACVR1 activity, where R206 is located. The GS domain is known to bind the regulatory protein FKBP12 and to undergo multiple phosphorylation events that trigger a signaling cascade inside the cell. The novel amino-acid substitution is predicted to influence either the conformation/stability of the GS region or the binding affinity with FKBP12, resulting in a less stringent inhibitory control on the ACVR1 kinase activity.**
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**Keywords:** FOP; *ACVR1*; heterotopic ossification; BMPs

## Introduction

Fibrodysplasia ossificans progressiva (FOP, MIM 135100) is a rare genetic disorder characterized by congenital malformations of the great toes and progressive heterotopic ossification causing the replacement of skeletal muscle and soft connective tissues with bone following a well-defined anatomic pattern.[1–3] FOP is the most severe and disabling disorder of heterotopic ossification in humans and leads to the formation of a second skeleton. Heterotopic ossification begins in childhood either spontaneously or following soft tissue injury and progresses in adulthood with typical episodic flare-ups and remissions.[1–3] The severe disability of FOP results in low

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## 1 - Titolo del Progetto di Ricerca

**Testo italiano**
*Meccanismi patogenetici dell'ossificazione eterotopica: il modello della Fibrodisplasia Ossificante Progressiva*

**Testo inglese**
*Pathogenic mechanisms of heterotopic ossification: the model of Fibrodysplasia Ossificans Progressiva*

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## 2 - Durata del Progetto di Ricerca

*24 Mesi*

# Attività di ricerca // Research activity

Svolta grazie al contributo economico dell'Associazione FOP Italia e del Ministero dell'Università

Carried out thanks to the economic contribution of FOP Italia and Italian Ministry of University

- mechanisms of ACVR1/ALK2 expression regulation
  - mRNA isoforms at the 5' UTR
  - regulation at 3' UTR
- cellular model for study of the SMAD-dependent BMP signaling

Proposed program in initial set up phase

cellular assay to test the effect of small chemical compounds on the SMAD-dependent signaling pathway

high throughput screening

A critical mass of scientific research is needed to obtain useful information for disease treatment

drug discovery?

Cells in which the mutant receptor is stably expressed

A GFP reporter regulated by a BRE is also stably expressed

Fluorescence is quantified by a plate reader

Hundreds of small chemical compounds can be screened for their effect on the signaling pathway

The Laboratory has accumulated good experience in screening of chemical compounds

Activators and inhibitors of CFTR, with potential application for treatment of Cystic Fibrosis and other diseases (Dr LV Galietta)

Equipment and methods will be transfered to screening for effectors of the BMP signaling pathway