

## **OR13-003 - TNFRSF11A molecular defects cause autoinflammatory disorders**

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MEETING ABSTRACT

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# OR13-003 - TNFRSF11A molecular defects cause autoinflammatory disorders

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## Introduction

Hereditary recurrent fevers (HRF) are autoinflammatory disorders whose etiology remains unknown in many cases.

## Objectives

To identify a new HRF gene

## Methods

Comparative genomic hybridization (CGH, 385K array) was performed in the proband. *TNFRSF11A* was screened by Sanger sequencing in other patients. *TNFRSF11A* expression was quantified by fluorescence-activated cell sorter analysis (FACS). NF- $\kappa$ B activation was assessed using a luciferase assay in HEK293 cells transfected with plasmids encoding wild-type and mutated *TNFRSF11A*.

## Results

Array-CGH analysis performed in a patient with multiple congenital anomalies and a recurrent fever syndrome revealed a *de novo* heterozygous chromosomal rearrangement encompassing a duplication of *TNFRSF11A*. This transmembrane receptor binds the TNFSF11 cytokine, activates NF- $\kappa$ B signaling, and regulates fever in rodents, consistent with a possible role in HRF. *TNFRSF11A* screening in other patients with genetically-unexplained HRF revealed a heterozygous frameshift mutation in a patient and her affected mother. The mutated protein is expressed at similar levels as the normal receptor on leukocytes. Most importantly, this mutation results in a gain of function on NF- $\kappa$ B signaling, since the mutated protein is more responsive to TNFSF11 stimulation than the wild-type receptor. Since *TNFRSF11A* (also known as *RANK*) was previously known for its key role in osteoclastogenesis,

the medical history of our patients was reassessed and revealed minor symptoms also found in patients with *TNFRSF11A*-associated bone disorders.

## Conclusion

The implication of *TNFRSF11A* in HRF reveals a key role of this receptor in autoinflammation and opens up new fields of research at the crossroads between bone metabolism and innate immunity.

## Disclosure of interest

None declared.

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