



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

I Jéru^{1,2,3*}, E Cochet³, P Duquesnoy¹, V Hentgen⁴, B Copin¹, M Mitjavila-Garcia⁵, S Sheykholeslami¹, G Le Borgne^{1,2}, F Dastot^{1,3}, S Karabina^{1,2}, M Mahevas⁶, S Chantot-Bastaraud¹, L Faivre⁷, S Amselem^{1,2,3}

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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- κ 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- κ 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- κ 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.

Authors' details

¹UMR_S933, INSERM, France. ²Université Pierre et Marie Curie-Paris, France. ³Génétique et d'Embryologie Médicales, Hôpital Trousseau, Paris, France. ⁴Centre de Référence des Maladies AutoInflammatoires (CeRéMAI), Centre Hospitalier de Versailles, Le Chesnay, France. ⁵U.935, INSERM, Villejuif, France. ⁶Médecine Interne, Hôpital Henri Mondor, Créteil, France. ⁷Centre de Génétique et Centre de Référence Anomalies du Développement et Syndromes Malformatifs, Hôpital d'Enfants, Dijon, France.

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¹UMR_S933, INSERM, France

Full list of author information is available at the end of the article