

## Evidence for a link between *TNFRSF11A* and risk of breast cancer

Núria Bonifaci · Marta Palafox · Pasquale Pellegrini · Ana Osorio · Javier Benítez · Paolo Peterlongo · Siranoush Manoukian · Bernard Peissel · Daniela Zaffaroni · Gaia Roversi · Monica Barile · Alessandra Viel · Frederique Mariette · Loris Bernard · Paolo Radice · Bella Kaufman · Yael Laitman · Roni Milgrom · Eitan Friedman · María E. Sáez · Fina Climent · María Teresa Soler · Orland Diez · Judith Balmaña · Adriana Lasa · Teresa Ramón y Cajal · María-Dolores Miramar · Miguel de la Hoya · Pedro Pérez-Segura · Trinidad Caldés · Víctor Moreno · Ander Urruticoechea · Joan Brunet · Conxi Lázaro · Ignacio Blanco · Miguel Angel Pujana · Eva González-Suárez

Received: 12 January 2011 / Accepted: 20 April 2011  
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**Abstract** Intracellular signaling mediated by the receptor activator of nuclear factor- $\kappa$ B [Rank, encoded by the tumor necrosis factor receptor superfamily, member 11a (*Tnfrsf11a*) gene] is fundamental for mammary gland development in mice, regulating the expansion of stem and progenitor cell compartments. Conversely, Rank overexpression in mice promotes abnormal proliferation and impairs differentiation, leading to an increased incidence of tumorigenesis. Here, we show that a common genetic variant near the 5'-end of *TNFRSF11A*, rs7226991, is associated with breast cancer risk in the general population and among carriers of mutations in the *breast cancer 2, early onset (BRCA2)* gene. Akin to the results of the Cancer and Genetics Markers of Susceptibility initiative,

combined analysis of rs7226991 in two Spanish case-control studies (1,365 controls and 1,323 cases in total) revealed a significant association with risk: odds ratio (OR) = 0.88, 95% confidence interval (CI) 0.78–0.98,  $P_{\text{trend}} = 0.025$ . Subsequent examination of *BRCA1* ( $n = 1,017$ ) and *BRCA2* ( $n = 885$ ) mutation carriers revealed a consistent association in the latter group: weighted hazard ratio ( $w$ HR) = 0.70; 95% CI 0.55–0.88; and  $P_{\text{trend}} = 0.003$ ; compared to *BRCA1* mutation carriers,  $w$ HR = 0.91; 95% CI 0.76–1.10; and  $P_{\text{trend}} = 0.33$ . The results of this study need to be replicated in other populations and with larger numbers of *BRCA1/2* mutation carriers.

Núria Bonifaci and Marta Palafox contributed equally to this work.

**Electronic supplementary material** The online version of this article (doi:10.1007/s10549-011-1546-7) contains supplementary material, which is available to authorized users.

N. Bonifaci · V. Moreno · M. A. Pujana (✉)  
Biomarkers and Susceptibility Unit, and Biomedical Research Center Network for Epidemiology and Public Health, Cancer Prevention and Control Program, Catalan Institute of Oncology, Bellvitge Institute for Biomedical Research (IDIBELL), Gran Via 199, L'Hospitalet, Barcelona 08908, Spain  
e-mail: mapujana@iconcologia.net

M. Palafox · P. Pellegrini · E. González-Suárez (✉)  
Cancer Epigenetics and Biology Program (PEBC), Bellvitge Institute for Biomedical Research (IDIBELL), Gran Via 199, L'Hospitalet, Barcelona 08908, Spain  
e-mail: egsuarez@idibell.cat

A. Osorio · J. Benítez  
Human Cancer Genetics Program and Biomedical Research Center Network for Rare Diseases, Spanish National Cancer Research Centre, Madrid, Spain

**Keywords** Breast cancer · *BRCA1/2* mutation carriers · RANK · *TNFRSF11A*

P. Peterlongo · P. Radice  
Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale Tumori, and IFOM Fondazione Istituto FIRC di Oncologia Molecolare, Milan, Italy

S. Manoukian · B. Peissel · D. Zaffaroni · G. Roversi  
Unit of Medical Genetics, Department of Preventive and Predictive Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale Tumori, Milan, Italy

M. Barile  
Division of Cancer Prevention and Genetics, Istituto Europeo di Oncologia, Milan, Italy