

SEARCH FOR NOVEL COMMON VARIANTS INFLUENCING DIFFERENTIATED THYROID CANCER

Gisella Figlioli^{1§}, Aleksandra Köhler^{2§}, Bowang Chen², Stefano Landi¹, Rossella Elisei³, Cristina Romei³, Monica Cipollini¹, Alfonso Cristaudo³, Franco Bambi⁴, Per Hoffmann^{5,6,7}, Stefan Herms^{5,6,7}, Michał Kalemba⁸, Dorota Kula⁸, Shelley Harris⁹, Peter Broderick⁹, Richard Houlston⁹, Susana Pastor^{10,11}, Ricard Marcos^{10,11}, Antonia Velázquez^{10,11}, Barbara Jarzab⁸, Kari Hemminki^{2, 12}, Asta Försti^{2, 12*}, Federica Gemignani^{1*}

¹Department of Biology, University of Pisa, Pisa, Italy; ²Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany; ³Department of Endocrinology and Metabolism, University of Pisa, Pisa, Italy; ⁴Blood Centre, Azienda Ospedaliero Universitaria A. Meyer, Firenze, Italy; ⁵Department of Genomics, Life and Brain Center, University of Bonn, Bonn, Germany; ⁶Institute of Human Genetics, University of Bonn, Bonn, Germany; ⁷Division of Medical Genetics, University Hospital Basel; Department of Biomedicine, University of Basel, CH-4058 Basel, Switzerland; ⁸Department of Nuclear Medicine and Endocrine Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, 44-101 Gliwice, Poland; ⁹Molecular and Population Genetics, Division of Genetics and Epidemiology, Institute of Cancer Research, Sutton, Surrey SM2 5NG, United Kingdom; ¹⁰Grup de Mutagènesi, Departament de Genètica i de Microbiologia, Facultat de Biociències, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallés, Barcelona, Spain; ¹¹CIBER Epidemiologia y Salud Pública, ISCIII, 28029 Madrid, Spain; ¹²Primary Health Care Research, Clinical Research Center, Lund University, 205 02 Malmö, Sweden

§G.F. and A.K. contributed equally to this work

*A.F. and F.G. contributed equally to this work

Thyroid cancer is a common endocrine malignancy with a rapidly increasing global incidence in the recent decades. Differentiated thyroid cancer (DTC), arising from follicular cells, includes the most common histological subtypes, papillary and follicular thyroid cancer, representing 80% and 15% of all thyroid cancers, respectively. Genome-wide association studies (GWASs) have identified robust associations with polymorphisms at 9q22.33 (*FOXE1*) and 14q13.2 (*NKX2-1*) and the disease. However, most of the inherited genetic risk factors of DTC remain to be discovered.

To search for new DTC risk variants we performed a GWAS in the high incidence Italian population and followed up the most significant associations in the lower incidence populations from Poland, UK and Spain. After excluding previously identified *loci*, the strongest association was observed for *DIRC3* at 2q35 ($P=6.4\times 10^{-10}$). Additionally promising associations were attained for *IMMP2L* at 7q31 ($P=4.1\times 10^{-6}$ and $P=5.7\times 10^{-6}$), *RARRES1* at 3q25.32 ($P=4.6\times 10^{-5}$) and *SNAPC4/CARD9* at 9q34.3 ($P=3.5\times 10^{-5}$).

Our findings provide insights into the genetic and biological basis of inherited genetic susceptibility to DTC. To further improve our knowledge on the disease, new *loci*, selected on the basis of association signals in our GWAS, will be analyzed.