



Giovanni Romeo

Director, Unit of Genetic Susceptibility to Cancer,
International Agency for Research on Cancer, Lyon,
France

CV

PROFESSIONAL EMPLOYMENT

- 1995-to date Chief, Unit of Genetic Cancer
Susceptibility, International Agency for
Research on Cancer, Lyon, France
- 1986-1995 Professor of Human Genetics - University
of Genoa Medical School
- Director of the Laboratory of Molecular
Genetics and Laboratory of Clinical
Cytogenetics, Istituto G. Gaslini
- 1978-86 Associate Professor of Molecular Genetics
- University of Bologna Medical School
- 1978-82 Lecturer in Genetics and Assistant
Professor - University of Bologna
- 1976-78 Visiting Scientist in the Department of
Genetics-Stanford Medical School
- Laboratory of Prof. L.L. Cavalli-Sforza
- 1972-78 Lecturer in Genetics - University of Naples
- 1972-76 Group leader of the Laboratory of Human

Genetics

- International Institute of Genetics and
Biophysics (I.I.G.B.) Naples
- 1968-71 Fellowship awarded by the Leukemia
Society of America for research on somatic
cell genetics and biochemical genetics in
the Division of Genetics of the Department
of Pediatrics of the Johns Hopkins Medical
School, Baltimore, MD - Laboratories of
Dr. E.Y. Levin and of Dr. B.R. Migeon
- 1966-69 Internship and residency in Pediatrics,
University of Bologna Medical School
- 1965 Certificate of the Educational Council for
Foreign Medical Graduates (ECMFG)
M.D. degree (with honours) from the
University of Bologna Medical School

HONOURS:

- Graduated cum Laude in Medicine,
University of Bologna (1965)
- Lepetit prize 1966, for M.D. thesis
- A.I.R.H. prize 1988, for work in human genetics

MEMBER OF THE FOLLOWING SCIENTIFIC SOCIETIES:

- European Society of Human Genetics
- President for 1991-1992
- Member of the Board (1990-95)
- American Society of Human Genetics (ASHG)
- Associazione Italiana di Genetica Medica (AIGM)
- EMBO (European Molecular Biology)

CONTACT INFORMATION

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Genetics of complex disorders: The RET Protooncogen and Thyroid Cancer

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Non-Medullary Thyroid Carcinoma (NMTC) accounts for ~90% of all thyroid cancers (prevalence adjusted for age=0.5-5/100,00 in most populations) and originates from the follicular cells of the thyroid. Papillary Thyroid carcinoma (PTC) and Follicular Carcinoma (FC) represent the two main variants of NMTC. Epidemiological studies demonstrate that a familial clustering of NMTC does exist. Familial NMTC (FNMTC) has been repeatedly observed clinically and it is characterized by a more aggressive behaviour than the sporadic cases. It follows an incompletely penetrant autosomal dominant mode of inheritance, and it is thought to represent ~5% of all cases of thyroid cancer. Very little is known about genetic predisposition to NMTC. On the other hand RET is found activated in 66% of sporadic PTC observed in Ukraine and Belarus 10 years after the Chernobyl accident. This activation derives from somatic mutations, namely chromosomal translocations or inversions resulting in rearrangements of the protooncogene RET with different genes.

In order to map genes predisposing to NMTC an International Consortium for the Genetics of FNMTC has been organized by IARC and 225 pedigrees have been collected. Two loci predisposing to FNMTC have been already identified: TCO (MIM [603386]) on 19p13.2, in a French family with an unusual form of NMTC with cell oxyphilia and PRN1 (MIM [605642]) on 1q21 in a US family with the most common form of NMTC, Papillary Thyroid Carcinoma (PTC) and Papillary Renal neoplasia. However, neither of these loci, nor the MNG1 (MIM [138800]) locus on 14q identified in a large Canadian family with multinodular goiter and low recurrence of NMTC account for a significant fraction of FNMTC pedigrees.

More recently in a large Tasmanian pedigree (Tas1) with recurrence of the most common form of NMTC, Papillary Thyroid Carcinoma (PTC), an extensive genome wide scan revealed a common haplotype on chromosome 2q21 in seven out of the eight PTC patients. In order to verify the significance of this 2q21 locus, linkage analy-

sis was performed in an independent sample set of 80 pedigrees yielding a multipoint HLOD of 3.07 ($\alpha=0.42$), NPL=3.19, ($p=0.001$) at marker D2S2271. Stratification based on the presence of at least one case of the follicular variant of PTC (fvPTC), the phenotype observed in the Tas1 family, identified 17 such pedigrees which showed a maximal HLOD score of 4.17 ($\alpha=0.80$), and an NPL=4.99 ($p=0.00002$) at markers AFMa272zg9 and D2S2271 respectively. These results indicate the existence of a new major susceptibility locus for FNMTC on chromosome 2q21.

In addition, six candidate genes, RET, TRK, MET, TSHR, APC, PTEN as well as TCO and MNG1 were excluded as major susceptibility genes in a large sample of families by using microsatellites that are positioned in or in close proximity to these genes. In order to determine if some variants of RET or a combination of them might predispose to PTC we looked for association of RET haplotype(s) in PTC cases and in controls matched for sex, age and population. Four single nucleotide polymorphisms (SNPs) across the RET coding sequence were typed and haplotypes reconstructed for sporadic PTC cases and controls using the Arlequin algorithm. Eleven unique haplotypes were obtained, which show a different breakdown in cases vs controls. Our data suggest that some variants of RET and some specific haplotypes are associated with predisposition to sporadic as well as familial PTC.