Bando Ricerca Finalizzata e Giovani Ricercatori, anno 2013

ROLE OF ENVIRONMENT-GENE INTERACTION IN ETIOLOGY AND PROMOTION OF PITUITARY TUMOURS

Progetto di Ricerca Ordinario

Principal Investigator (PI): Salvatore Cannavò[1]

Componenti gruppo di Ricerca: Felice Esposito[2], Laura Rosa Pisani[3], Filippo Flavio Angileri[2], M'Hamed Aguennouz[2]

[1]UOC di Endocrinologia, AOU Policlinico Gaetano Martino di Messina, [2]Dipartimento di Neuroscienze, Università di Messina, [3]IRCCS Centro Neurolesi Bonino-Pulejo, Messina

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INTRODUZIONE E STATO DELL'ARTE

Questo progetto studia il ruolo della via di segnale del recettore per gli idrocarburi arilici (AHR), che può essere attivata da diverse sostanze xenobiotiche (XBSs), in relazione allo sviluppo, alle caratteristiche biologiche ed alla risposta ai farmaci degli adenomi ipofisari (AI) che causano acromegalia. Il progetto origina dalla evidenza di un'aumentata prevalenza di acromegalia in un'area della Sicilia identificata come sito di interesse nazionale ad alto rischio per la salute, e dal riscontro di adenomi ipofisari più aggressivi in pazienti portatori di uno specifico polimorfismo del gene AHR.

Recentemente, abbiamo dimostrato che un polimorfismo del gene codificante per AHR, responsabile di una maggiore affinità delle XBSs al recettore stesso, è più frequente nei pazienti acromegalici rispetto alla popolazione generale ed è associato alla presenza di AI più invasivi ed ad un maggior rischio di neoplasie secondarie (1). Inoltre, insieme ad altri autori, abbiamo anche dimostrato che mutazioni germinali del gene che codifica per AHR-Interacting-Protein (AIP), predispongono allo sviluppo di AI, sia in forma familiare, che sporadica (2-4). Spesso, questi tumori si dimostrano aggressivi e resistenti agli analoghi della somatostatina (SSA) (5).

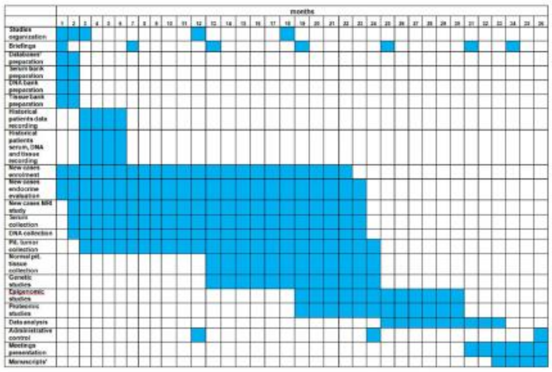
Il nostro gruppo ha coordinato un network di ricerca (PRIN 2010-2011) sullo stesso argomento cui partecipano le scuole di Endocrinologia delle Università di Torino, Milano (Statale), Padova, Ferrara e Pisa, la scuola di Neurochirurgia dell'Università Vita-Salute San Raffaele di Milano e il laboratorio di Neuroscienze del CNR di Roma.

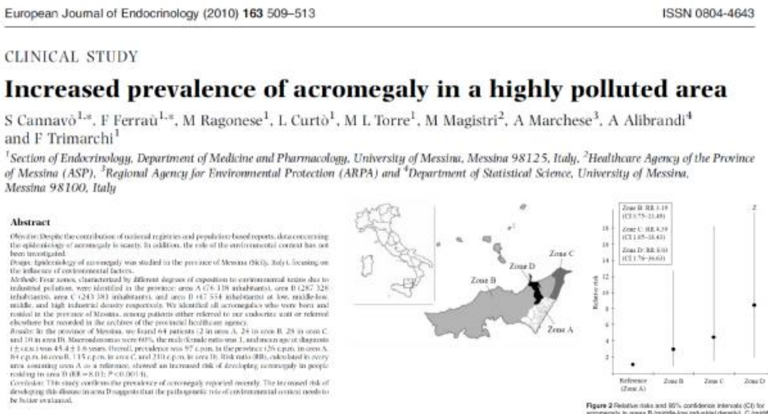
OBIETTIVI DELLA RICERCA

Obiettivo 1: valutare la frequenza delle varianti in omozigosi e in eterozigosi di AHR e di altri geni che codificano per le proteine coinvolte nei meccanismi di detossificazione delle XBSs nei pazienti con acromegalia.

Obiettivo 2: indagare gli effetti epigenetici (metilazione, deacetilazione) dovuti all'esposizione alle XBSs sulla espressione di geni coinvolti nella via di segnale di AHR nel tessuto tumorale e nel tessuto ipofisario sano, in pazienti acromegalici ed in modelli animali.

Obiettivo 3: studiare l'espressione di miRNA e proteine (ormoni, enzimi) correlati alle alterazioni della *pathway* di AHR nel tessuto tumorale dei pazienti acromegalici, mediante un approccio proteomico.





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CLINICAL STUDY

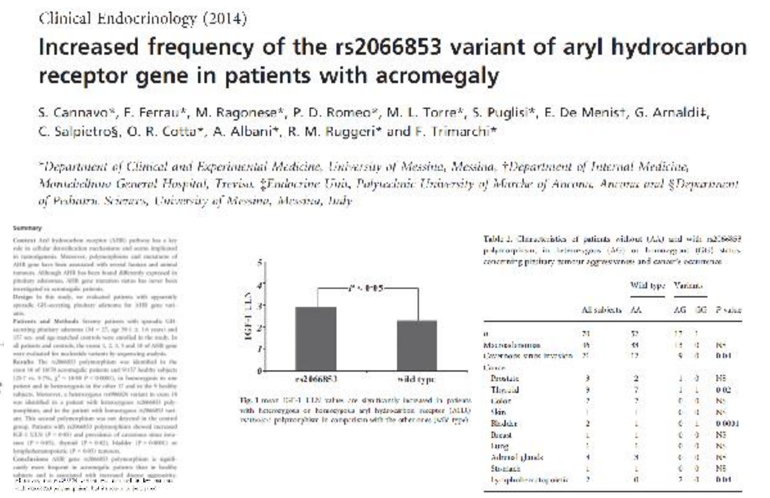
Increased prevalence of acromegaly in a highly polluted area

S Cannavò[1,*], F Ferraù[1,*], M Ragonese[1], L Curtò[1], M L Torre[1], M Magistri[2], A Marchese[3], A Alibrandi[4] and F Trimarchi[1]

[1]Section of Endocrinology, Department of Medicine and Pharmacology, University of Messina, Messina 98125, Italy, [2]Healthcare Agency of the Province of Messina (ASP), [3]Regional Agency for Environmental Protection (ARPA) and [4]Department of Statistical Science, University of Messina, Messina 98100, Italy

Abstract

Figure 2 Relative risks and 95% confidence intervals (CI) for acromegaly in areas B (middle-low industrial density), C (middle industrial density), and D (high industrial density), assuming the population of area A (low industrial density) as a reference.



Clinical Endocrinology (2014)

Increased frequency of the rs2066853 variant of aryl hydrocarbon receptor gene in patients with acromegaly

S. Cannavo*, F. Ferrau*, M. Ragonese*, P. D. Romeo*, M. L. Torre*, S. Puglisi*, E. De Menis†, G. Arnaldi‡, C. Salpietro§, O. R. Cotta*, A. Albani*, R. M. Ruggeri* and F. Trimarchi*

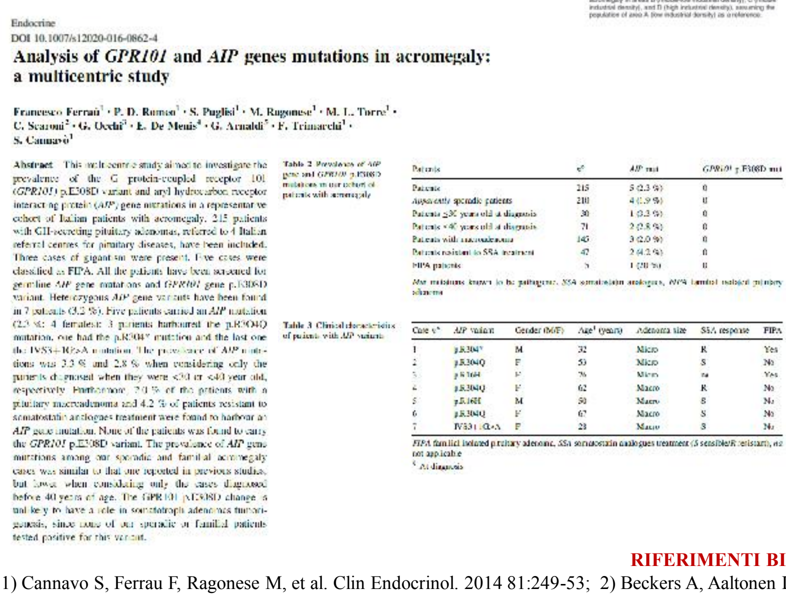
**Department of Clinical and Experimental Medicine, University of Messina, Messina, †Department of Internal Medicine, Montebelluno General Hospital, Treviso, ‡Endocrine Unit, Polytechnic University of Marche of Ancona, Ancona and §Department of Pediatric Sciences, University of Messina, Messina, Italy*

Summary

Fig. 1 mean IGF-1 ULN values are significantly increased in patients with heterozygous or homozygous aryl hydrocarbon receptor (AHR) variant polymorphism in comparison with the other ones (wild type).

Table 1. Characteristics of patients without (AA) and with rs2066853 polymorphism, in heterozygous (AG) or homozygous (GG) status, concerning pituitary tumour aggressiveness and cancer's occurrence

	All subjects	Wild type AA	Variants AG	GG	P value
n	[illegible]	[illegible]	[illegible]	1	
Macroadenomas	[illegible]	[illegible]	[illegible]	0	NS
Cavernous sinus invasion	[illegible]	[illegible]	9	0	0·04
Cancer					
Prostate	3	2	1	0	NS
Thyroid	9	7	1	1	0·02
Colon	2	2	0	0	NS
Skin	1	1	0	0	NS
Bladder	2	1	0	1	0·0001
Breast	1	1	0	0	NS
Lung	1	1	0	0	NS
Adrenal glands	4	3	0	0	NS
Stomach	1	1	0	0	NS
Lymphohaematopoietic	2	0	2	0	0·04



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Analysis of *GPR101* and *AIP* genes mutations in acromegaly: a multicentric study

Francesco Ferraù[1] · P. D. Romeo[1] · S. Puglisi[1] · M. Ragonese[1] · M. L. Torre[1] · C. Scaroni[2] · G. Occhi[3] · E. De Menis[4] · G. Arnaldi[5] · F. Trimarchi[1] · S. Cannavò[1]

Abstract This multicentric study aimed to investigate the prevalence of the G protein-coupled receptor 101 (*GPR101*) p.E308D variant and aryl hydrocarbon receptor interacting protein (*AIP*) gene mutations in a representative cohort of Italian patients with acromegaly. 215 patients with GH-secreting pituitary adenomas, referred to 4 Italian referral centres for pituitary diseases, have been included. Three cases of gigantism were present. Five cases were classified as FIPA. All the patients have been screened for germline *AIP* gene mutations and *GPR101* gene p.E308D variant. Heterozygous *AIP* gene variants have been found in 7 patients (3.3 %). Five patients carried an *AIP* mutation (2.3 %: 4 females): 3 patients harboured the p.R304Q mutation, one had the p.R304* mutation and the last one the IVS3+1G>A mutation. The prevalence of *AIP* mutations was 3.3 % and 2.8 % when considering only the patients diagnosed when they were ≤30 or ≤40 year old, respectively. Furthermore, 2.0 % of the patients with a pituitary macroadenoma and 4.2 % of patients resistant to somatostatin analogues treatment were found to harbour an *AIP* gene mutation. None of the patients was found to carry the *GPR101* p.E308D variant. The prevalence of *AIP* gene mutations among our sporadic and familial acromegaly cases was similar to that one reported in previous studies, but lower when considering only the cases diagnosed before 40 years of age. The GPR101 p.E308D change is unlikely to have a role in somatotroph adenomas tumorigenesis, since none of our sporadic or familial patients tested positive for this variant.

Table 2 Prevalence of *AIP* gene and *GPR101* p.E308D mutations in our cohort of patients with acromegaly

Patients	n°	*AIP* mut	*GPR101* p.E308D mut
Patients	215	5 (2.3 %)	0
Apparently sporadic patients	210	4 (1.9 %)	0
Patients ≤30 years old at diagnosis	30	1 (3.3 %)	0
Patients ≤40 years old at diagnosis	71	2 (2.8 %)	0
Patients with macroadenoma	145	3 (2.0 %)	0
Patients resistant to SSA treatment	47	2 (4.2 %)	0
FIPA patients	5	1 (20 %)	0

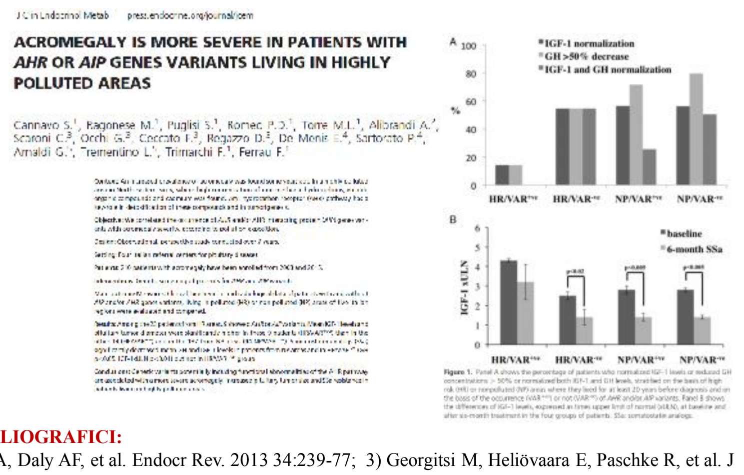
Mut mutations known to be pathogenic, *SSA* somatostatin analogues, *FIPA* familial isolated pituitary adenoma

Table 3 Clinical characteristics of patients with *AIP* variants

Case n°	*AIP* variant	Gender (M/F)	Age[§] (years)	Adenoma size	SSA response	FIPA
1	p.R304*	M	32	Micro	R	Yes
2	p.R304Q	F	53	Micro	S	No
3	p.R16H	F	76	Micro	na	Yes
4	p.R304Q	F	62	Macro	R	No
5	p.R16H	M	50	Macro	S	No
6	p.R304Q	F	67	Macro	S	No
7	IVS3+1G>A	F	28	Macro	S	No

FIPA familial isolated pituitary adenoma, *SSa* somatostatin analogues treatment (*S* sensible/*R* resistant), *na* not applicable

[§] At diagnosis



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ACROMEGALY IS MORE SEVERE IN PATIENTS WITH *AHR* OR *AIP* GENES VARIANTS LIVING IN HIGHLY POLLUTED AREAS

Cannavo S.[1], Ragonese M.[1], Puglisi S.[1], Romeo P.D.[1], Torre M.L.[1], Alibrandi A.[2], Scaroni C.[3], Occhi G.[3], Ceccato F.[3], Regazzo D.[3], De Menis E.[4], Sartorato P.[4], Arnaldi G.[5], Trementino L.[5], Trimarchi F.[1], Ferrau F.[1]

Figure 1. Panel A shows the percentage of patients who normalized IGF-1 levels or reduced GH concentrations > 50% or normalized both IGF-1 and GH levels, stratified on the basis of high risk (HR) or nonpolluted (NP) areas where they lived for at least 20 years before diagnosis and on the basis of the occurrence (VAR+/+) or not (VAR-/-) of AHR and/or AIP variants. Panel B shows the differences of IGF-1 levels, expressed as times upper limit of normal (xULN), at baseline and after six-month treatment in the four groups of patients. SSa: somatostatin analogs.

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