



Associazione
Italiana
Radioterapia
Oncologica



Il ruolo dei polimorfismi del gene del recettore 4 delle melanocortine (MC4R) nei pazienti affetti da glioblastoma multiforme

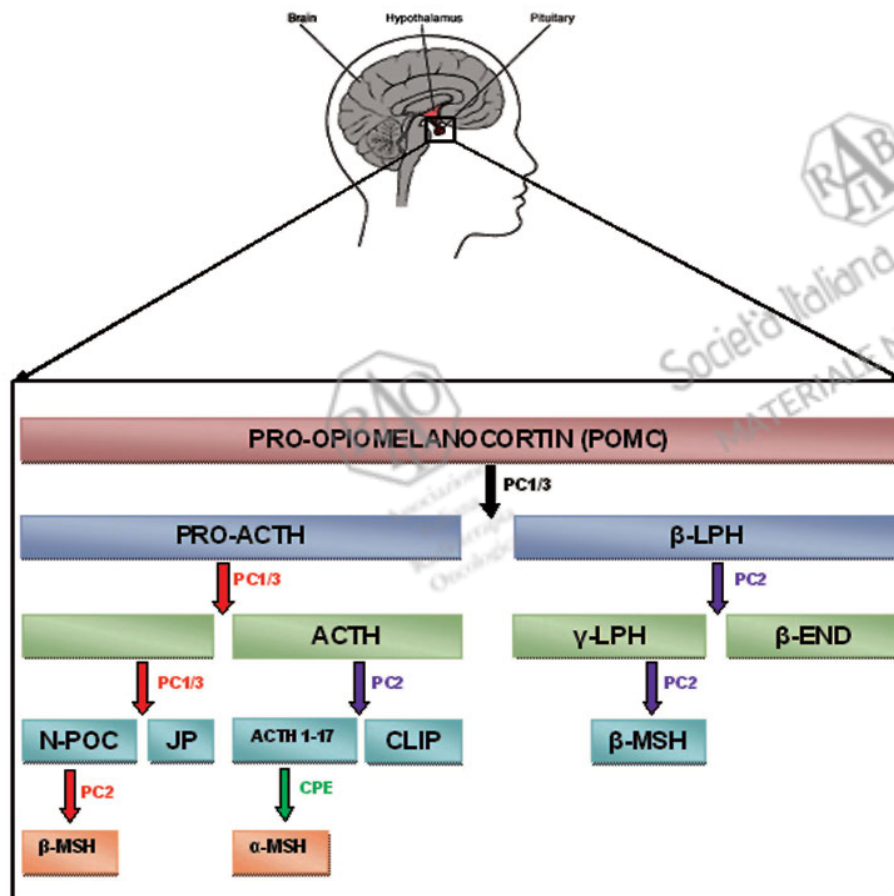
*Martina Cantarella
UO Radioterapia Oncologica
Pisa*



Le melanocortine

Peptidi di origine endogena derivati da un precursore comune di origine ipofisaria:

PROOPIOMELANOCORTINA (POMC)



Azione mediata dal legame con cinque classi di recettori trans-membrana

Receptor	Distribution	Endogenous agonists	Endogenous antagonists	Function
MC1R	- Dermal fibroblasts - Keratinocytes - Melanocytes - Neutrophils - Monocytes - B lymphocytes - Macrophages - Endothelial cells - Dendritic cells - Olfactory cells - Astrocytes	α-MSH, β-MSH and ACTH have higher affinity than γ-MSH	Agouti	- Nociception - Anti-inflammatory - Skin pigmentation
MC2R	- Adrenal cortex - Melanocytes - Keratinocytes - Adipose tissue - Bone cells	ACTH	Agouti	Steroidogenesis
MC3R	- CNS - Stomach - Duodenum - Kidneys - Placenta - Heart - Monocytes - Macrophages	α-MSH, β-MSH, γ-MSH and ACTH	AGRP	- Energy homeostasis - Food intake - Anti-inflammatory
MC4R	- Cortex - Thalamus - Hypothalamus - Hippocampus - Brainstem - Spinal cord - Astrocytes - Heart - Lung - Kidney - Testis	α-MSH, β-MSH and ACTH have higher affinity than γ-MSH	Agouti and AGRP	- Energy homeostasis - Food intake - Anti-inflammatory - Nociception - Memory - Mood disorders - Neuroprotection - Drug addiction - Drug tolerance - Sexual behaviour
MCSR	- Skin - Spleen lung - Cut - Sexual organs - Bone marrow - Adipose tissue	α-MSH has higher affinity than β-MSH and ACTH, both of which have higher affinity than γ-MSH	Agouti	- Exocrine secretion - Lipid mobilization

Astrocytes: new targets of melanocortin 4 receptor actions

Carla Caruso, Lila Carniglia, Daniela Durand, Teresa N Scimonelli¹ and Mercedes Lasaga

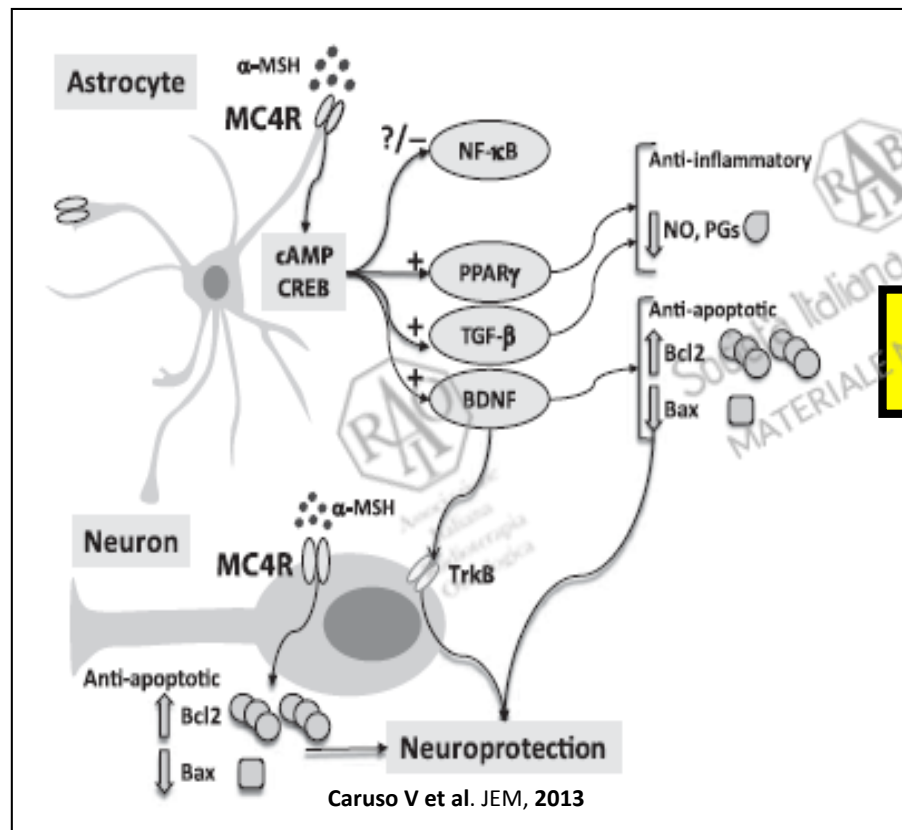
School of Medicine, Biomedical Research Institute (UBA-CONICET), University of Buenos Aires, Paraguay 2155 piso 10, 1121ABG Buenos Aires, Argentina

¹IFEC (CONICET) Department of Pharmacology, School of Chemistry, National University of Córdoba, Córdoba, Argentina

Correspondence should be addressed to M. Lasaga
Email: mlasaga@fmed.uba.ar

Effect on	MC4R agonist or antagonist action	References
Energy homeostasis	α - and β -MSH decrease food intake MTII agonist reduces food intake and increases metabolic rate AGRP antagonist increases food intake	Abbott <i>et al.</i> (2000) Chen <i>et al.</i> (2000b) Rossi <i>et al.</i> (1998)
Sexual function	THIQ agonist increases erectile activity and enhances copulatory behavior MTII induces and SHU9119 completely blocks penile erection	Van der Ploeg <i>et al.</i> (2002) Wessells <i>et al.</i> (2003)
Reproduction	MTII agonist increases luteinizing hormone and prolactin secretion in female fasted rats AGRP reduces luteinizing hormone and prolactin surge in female fasted rats AGRP induces luteinizing hormone and follicular stimulating hormone release in male rats	Schioth <i>et al.</i> (2001) Watanobe <i>et al.</i> (2001) Stanley <i>et al.</i> (1999)
Cachexia	MC4R function restores pubertal onset, fertility, and lactation in mice AGRP attenuates cardiac cachexia in heart failure and in mice-bearing tumor Small-melanocortin inhibitors attenuate cachexia	Israel <i>et al.</i> (2012) Scarlett <i>et al.</i> (2010) Joppa <i>et al.</i> (2007) DeBoer (2010)
Pain	MTII increases and antagonist SHU9119 decreases sensitivity to pain AGRP reduces mechanical allodynia in a model of chronic pain in rats	Starowicz <i>et al.</i> (2002) Bertorelli <i>et al.</i> (2005)
Neuroprotection	H5024-selective MC4R antagonist blocks NDP-MSH protective effect on cerebral ischemia MC4R antagonist prevents the increase in neurite outgrowth induced by α -MSH in Neuro2A cells	Giuliani <i>et al.</i> (2006) Giuliani <i>et al.</i> (2009) Adan <i>et al.</i> (1996)
Memory	H5014 blocks α -MSH-induced recovery from memory impairment produced by IL1 β in rats NDP-MSH improves memory and learning of gerbils	Gonzalez <i>et al.</i> (2009) Machado <i>et al.</i> (2010) Giuliani <i>et al.</i> (2011)
Inflammation	H5024 blocks α -MSH-induced reduction of iNOS and COX2 expression induced by LPS in rat hypothalamus and by LPS + IFN- γ in astrocytes	Caruso <i>et al.</i> (2004) Caruso <i>et al.</i> (2007)
Fever	Selective MC4R agonist MRLOB-001 suppresses LPS-induced fever H5014 blocks α -MSH anti-pyretic effect	Sinha <i>et al.</i> (2003) Sinha <i>et al.</i> (2004)

MC4R



RUOLO NEL MEDIARE
LA RISPOSTA AL
DANNO INDOTTO DA
RADIAZIONI
IONIZZANTI

RAZIONALE

- Valutare la relazione tra **MC4R - SNPs** e **PFS/OS** di pazienti con GBM trattati con RTCT
- Valutare relazione tra **MC4R - SNPs** e **PFS/OS** in pazienti con GBM che effettuano terapie di II linea (CT-anti VEGF)

MATERIALI E METODI

**61 pz con diagnosi patologica di GBM
(Marzo 2016)**

CRITERI DI INCLUSIONE

- Diagnosi istologica GBM
- Disponibilità al prelievo ematico
- Età > 18 anni
- Buon PS (ECOG 0-2)
- Candidabili a trattamenti RT e/o CT di I e II linea

- ✓ Età media 57 aa (24-80)
- ✓ 50 pz RTCT sec. STUPP
- ✓ 6 pz no RT
- ✓ 43 pz CT di II linea

CRITERI DI ESCLUSIONE

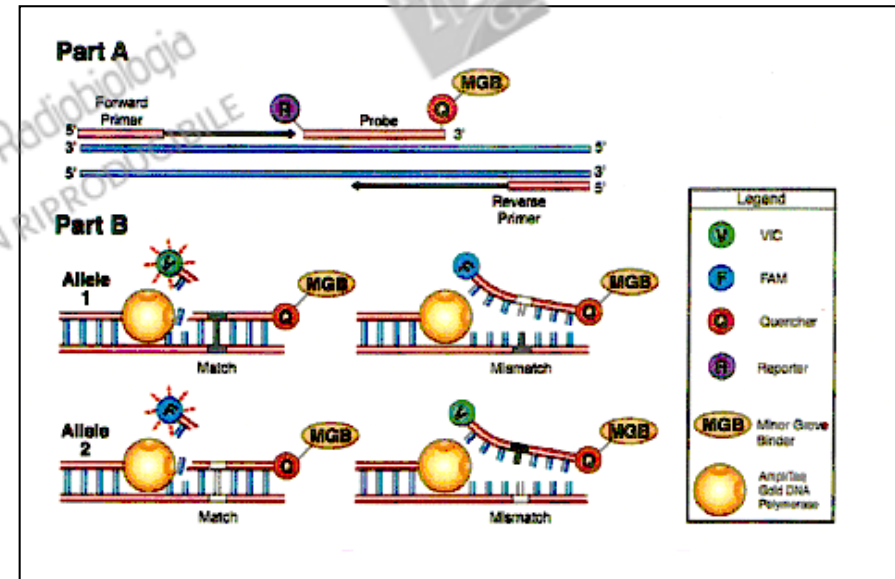
- Pregressi trattamenti RT e/o CT su SNC

RM con mdc ogni 3 mesi

**13 pz ancora in vita
marzo 2016**

MATERIALI E METODI

- 3 ml sangue venoso
- Trattati mediante l'aggiunta di EDTA e conservati in ambiente refrigerato alla temperatura di -80°C .
- Estrazione del DNA
- Ricerca ed amplificazione delle sequenze di interesse mediante RealTime PCR (SNP)



MATERIALI E METODI

Sequenza rs17782313

GTTTAAAGCAGGAGAGATTGTATCC[C/T]

GATGGAAATGACAAGAAAAGCTTCA

Allele Ancestrale T, Allele Mutato C

Sequenza rs489693

TCTTAATTCTGTTGTCATTAGTTCC[A/C]

GTTTGTAAATGTTTACAGCGTGGC

Allele Ancestrale A, Allele Mutato C

Sequenza rs8087522

TAAGAACCCAGCCAGTAGTGGTTCA[A/G]

TTAAAATACCTGAAAAACAGAGAGG

Allele Ancestrale A, Allele Mutato G

Sequenza rs17700633

GTTTCACTGTGTGGCAAGACAGAAT[A/G]

TGTGGTACCCGGTCGCTGCTAAGG

Allele Ancestrale A, Allele Mutato G

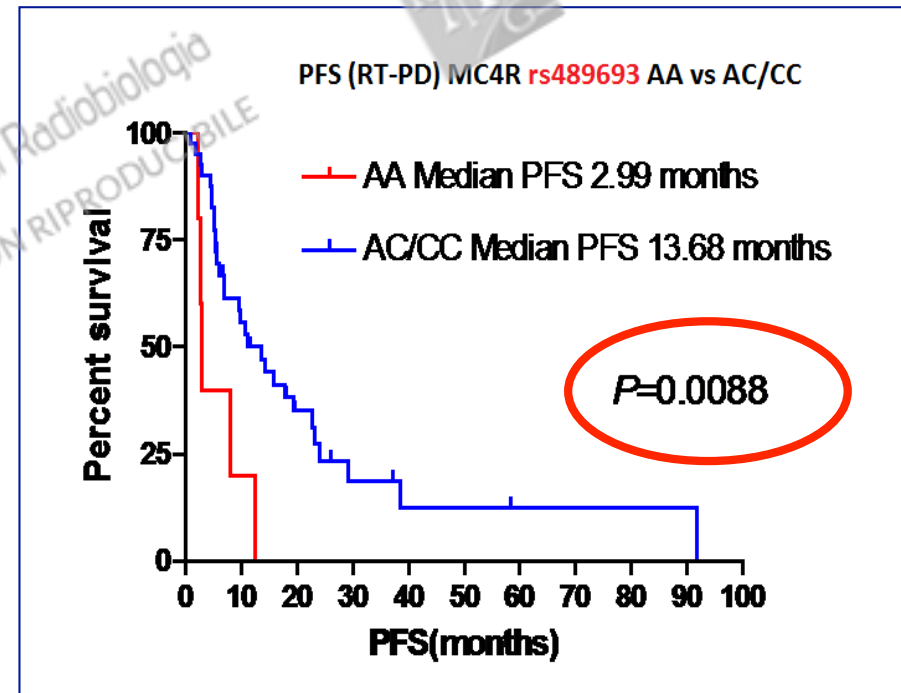
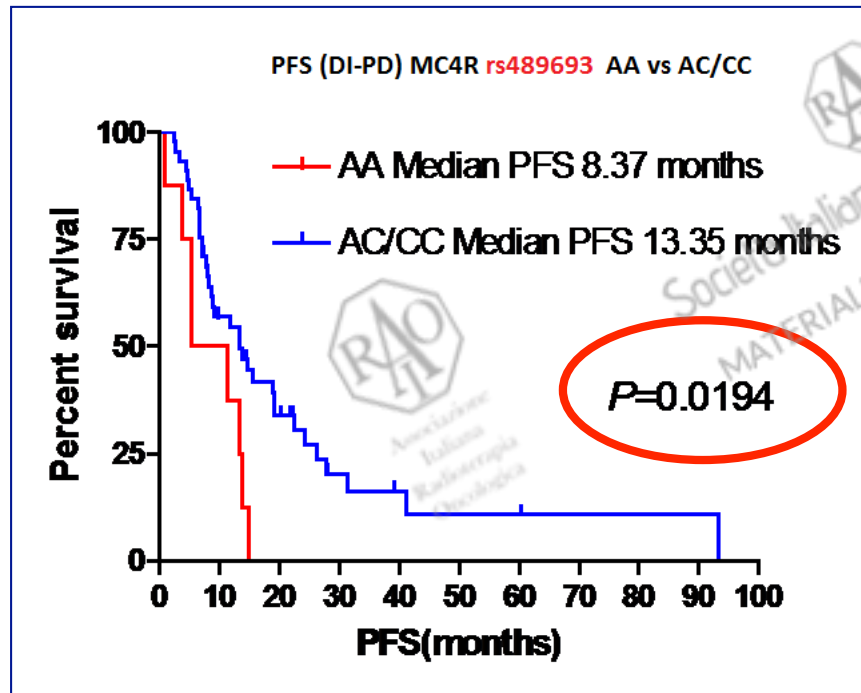
SNPs	GENOTIPO	FREQ. GENICA (%)	FREQ. ALLELICA (%)
MC4R C/T rs17782313	4 CC 27 CT 30 TT	CC: 6.56 CT: 44.26 TT: 49.18	35 C:28.69 87 T: 71.31
MC4R A/C rs489693	9 AA 24 AC 28 CC	AA:14.75 AC:39.34 CC:45.91	42 A: 34.43 80 C:65.57
MC4R A/G rs8087522	6 AA 21 AG 34 GG	AA:9.84 AG:34.43 GG:55.73	33 A:27.05 89 G:72.95
MC4R A/G rs17700633	3 AA 22 AG 36 GG	AA:4.92 AG:36.06 GG:59.02	28 A:22.95 94 G:77.05

EQUILIBRIO DI HARDY-WEINBERG:

le frequenze alleliche in una grande popolazione rimangono costanti di generazione in generazione o si modificano in seguito a fenomeni evolutivi.

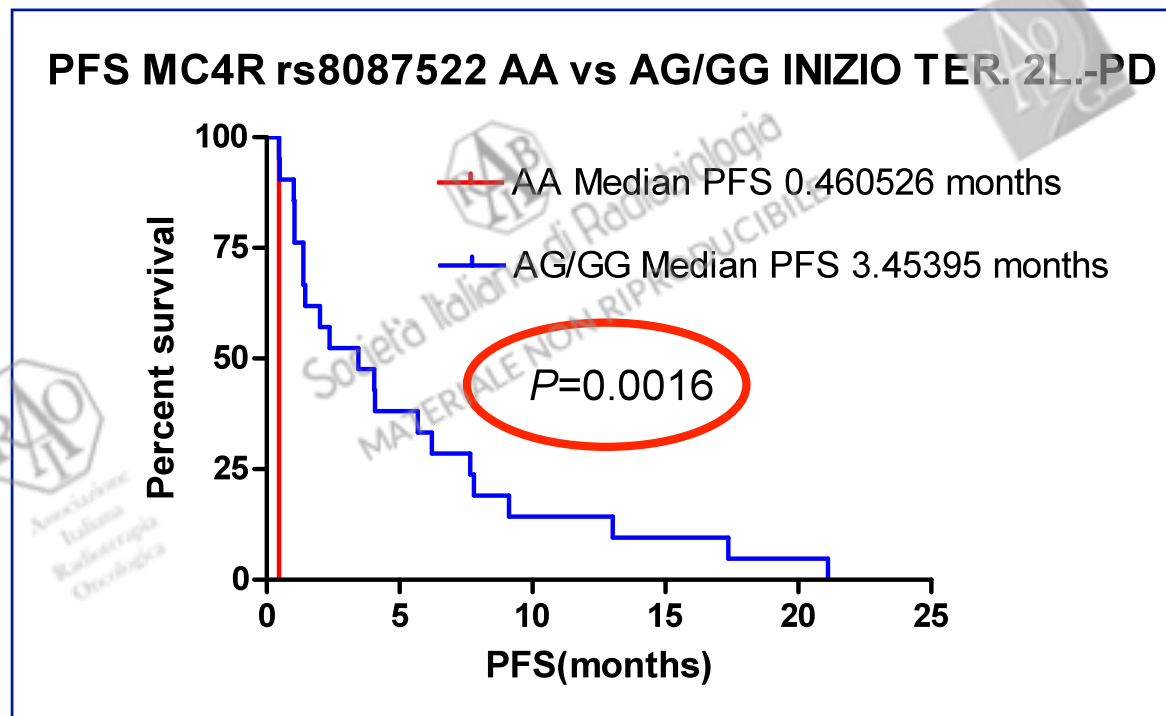
RISULTATI

PFS dei soggetti omozigoti per l'allele ancestrale (AA) del rs 489693



RISULTATI

PFS dei soggetti omozigoti per l'allele ancestrale (AA) del rs 8087522



OS omozigoti (AA) rs 489693 inferiore rispetto eterozigoti (AC/CC) ($p= 0.274$)

CONCLUSIONI

- ✓ Risultati promettenti si sono ottenuti analizzando le curve di sopravvivenza relative a **rs 489693** e a **rs 8087522**
- ✓ I risultati ottenuti al momento devono essere confermati per poter meglio definire il ruolo dei polimorfismi analizzati come sicuro indice prognostico o di risposta al trattamento



incremento numerico del campione!



Associazione
Italiana
Radioterapia
Oncologica



GRAZIE PER L'ATTENZIONE