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ARE THE GENES CA6, TAS2R38, TCF7L2, FTO, TAS1R2, TAS1R3, GNAT3 RECEPTOR POLYMORPHISMS INVOLVED ON EXCEPTIONAL LONGEVITY AND RISK OF SARCOPENIA? A CROSS SECTIONAL STUDY IN ITALIAN AGING POPULATION

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Perna S. (2020). *Are the genes CA6, TAS2R38, TCF7L2, FTO, TAS1R2, TAS1R3, GNAT3 receptor polymorphisms involved on exceptional longevity and risk of sarcopenia? A cross sectional study in Italian aging population*.- Genetika, Vol 52, No.1, 177-186.

This study hypothesized that genetic polymorphisms of different genes could modulate the lifespan and muscle health or sarcopenia. We investigated the possible associations between longevity and the common genetic variation polymorphism such as rs713598, rs7903146, rs9939609, rs35874116, rs2274333, rs7792845, rs35744813 in a population of 360 Italian elderly aged 65- 100 years. The polymorphism rs9939609, of the FTO gene, shows an association ($p< 0.001$) with longevity. In particular, the frequency of T/T homozygotes increases gradually from 35% in subjects aged 65-80 ys up to 80% in centenarians. The polymorphism of rs2274333 (CA6) gene shows that A/G frequency increases continuously through older classes reaching the 80% in (95-100) (p trend <0.05). Another important founding regards the polymorphism of rs35744813 of TAS1R3 gene. The C/C genotype frequency is over 80% in all classes (65–95 years) but appears increase in oldest old and reach 100% (95-100 ys). While T allele frequency decrease continuously through older classes reaching the 0% in T/T and 5% in C/T in (95-100) (p-trend <0.05). These data provide suggestive evidence on the possible correlation between longevity and FTO gene (obesity related), CA6 gene (the gustin-bitter taste related) and TAS1R3 (umami taste stimulus related). None associations with sarcopenia were detected.

Keywords: genes, polymorphism, sarcopenia, longevity.

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INTRODUCTION

Currently the missing bridge between longevity and genetic is under evaluation in different countries and involve several epidemiological studies. Longevity studies are widespread in Italy due to a higher level of oldest old elderly (shared with Japan) and the upper life expectantly. This ecological and epidemiological cross-sectional study has been performed in order to assess the relationship between different gene polymorphism (a gene polymorphism is defined as the regular occurrence (>1%) in a population of two or more alleles at a particular chromosome location), longevity and muscle health. This study explores the Genes CA6, TAS2R38, TCF7L2, FTO, TAS1R2, TAS1R3, GNAT3 polymorphisms in order to discover any relationship on life expectantly.

As regards, previous studies recently has been showed that a polymorphism in the gene CA6 coding for the salivary trophic factor, gustin or Carbonic Anhydrase 6 (CA6), affects PROP sensitivity by acting on cell growth and fungiform papillae maintenance and liking and intake of Brassicaceous vegetables and related antioxidants intake are influenced by bitter taste sensitivity (SHEN *et al*., 2016). Studies on centenarians or long-lived subjects allowed indeed to identify specific genes and genotypes involved in these pathways that influence human lifespan (BONAFÈ and OLIVIERI, 2009; CHUNG *et al*., 2010; SLAGBOOM *et al*., 2011). A recent studiTAS2R38 genotype correlates both with quality of life scores and rhinologic-specific QOL in homozygous the cystic fibrosis patients (ADAPPA *et al*., 2016).

Recent gene polymorphism such as rs713598 gene, TAS2r38 rs7903146 TCF7L2 Gene, rs9939609 FTO gene, rs35874116 TAS1R2 gene, rs2274333 (CA6) gene, rs7792845 GNAT3 gene, and rs35744813 TAS1R3 gene are of recent interest in different cutting edge endevours. While for genotype rs7792845 (near the gene GNAT3), an effect on sweet and acid perception has been disclosed; the increase of the G allele corresponds to an increase (responsiveness decrease) of the sensitivity to the sweet (responsiveness acid) taste. But until now no data on longevity are available (SIA *et al*., 2013). For example recently with the use of a Mendelian randomization approach to directly assess the effect of genetic variability on the perception of wine tastes. We observed two potentially relevant signals, namely the associations between the *TAS2R38* SNPs and *TAS2R16*-rs6466849 with wine bitterness and sourness respectively (CARRAI *et al*., 2017).

Regarding rs7903146 The most interesting result of a recent study involves the rs7903146 located in the TCF7L2 gene. Genotypic frequencies of this SNP vary proportionally according to the decrease of health/longevity and the increase of T2D severity (GIULIANI *et al*., 2017).

Rs9939609 FTO increases in adolescent and early adulthood BMI were generally not associated with, or were associated with lower levels, of affective symptoms in the *FTO* risk homozygote (AA) group, but positive associations were seen in the TT group (KOIKE *et al*., 2018).

Recent funding in term of lifespan suggest that there is a genetic connection between TCF7L2 and related factors with Hereditary Multiple Exostoses . This study suggest that genetic variation in this context possibly modulates shared pathways, in particular with respect to ß-catenin, leading to a potential interplay that influences HME pathogenesis as well as that of T2D.

Even the connection between sarcopenia, a progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls,

fractures, physical disability and mortality. and genes expression is under investigation by several studies. As showed recently by a recent study, the BMI, physical activity, protein and selenium intake are mildly associated with sarcopenia-related DNA methylation in promoter regions, indicating their possible influence on sarcopenia (HE *et al*., 2019).

Regarding the relationship between FTO gene and longevity, a recent study confirmed the association between body weight and the *FTO*rs9939609 polymorphism. Interestingly, our results showed that, although at baseline the A allele was associated with higher body weight, after 3 years of nutritional intervention with a Mediterranean-style-diet, A-allele carriers had lower body weight gain than wild type subjects and a possible increase of lifespan (RAZQUIN *et al*., 2013).

Finally the TAS2R and TAS1R genetic polymorphisms seem to play a role in the human longevity (CAMPA *et al*., 2012). This study showed with bar chart of age by genotypes showing the association between the polymorphism of TAS2R16 rs 978739 and longevity. But no other studies are available.

We hypothesized that genetic polymorphisms of different genes could modulate the lifespan and muscle health or sarcopenia. We investigated the possible associations between longevity and the common genetic variation polymorphism such as rs713598, rs7903146, rs9939609, rs35874116, rs2274333, rs7792845, rs35744813 in a population of 360 Italian elderly aged 65- 100 years.

MATERIALS AND METHODS

Subjects

This is across-sectional study. Adults aged 65-110 years, with body mass index (BMI) 15–35 kg/m^2), who were admitted to the *Azienda di Servizi alla Persona di Pavia*, University of were prospectively enrolled. All subjects had to give complete medical histories, and received a physical examination, with anthropometric assessment and routine laboratory tests. The study was conducted with the approval of the Ethics Committee of the Department of Internal Medicine and Medical Therapy, at the University of Pavia. Subjects gave written consent to participate in the study.

Genetic markers

Tag SNPs in genes likely to be involved in the human sweet and bitter taste receptor system were selected with the Tagger programme within Haploview software (BARRETT *et al*., 2005; CARRAI *et al*., 2011).

The resulting SNPs captured genetic variability in four chromosome regions of interest, as previously suggested (BOUTHOORN *et al*., 2014; DOTSON *et al*., 2010); namely rs713598 in the TAS2R38 gene, and rs7792845 (near the gene GNAT3) on chromosome 7, rs7903146 (TCF7l2 gene) on chromosome 10 and rs2274333 (CA6 gene) on chromosome 1.

DNA was extracted from buccal swabs following the Invisorb® Spin Swab KitIl protocol (BALOGH *et al*., 2003). This simple procedure comprises the following steps: lysis of cells with standard proteinase K, binding the genomic DNA to the membrane of a Spin Filter, washing the membrane then elution of genomic DNA. All genotyping was carried out using Kaspar

(Kbioscience, Heddesdon, UK) (VON WURMB-SCHWARK *et al*., 2006). Assay PCR plates read on a ViiA 7RUO Software instrument (Applied Biosystems) (GURRAMKONDA *et al*., 2015).

Blood samples

Fasting venous blood samples were drawn between 8 and 10 a.m., with the subjects seated. Blood was collected and handled under strictly standardized conditions. Serum albumin was analysed using a nephelometric method (Behring nephelometric analyzer II; Behring Diagnostics GmbH, Marburg, Germany) (LIZANA *et al*., 1974**)**, with a 2% coefficient of variation. Fasting blood total cholesterol and triglycerides were measured with an automatic biochemical analyzer (Hitachi 747; Hitachi Ltd., Tokyo, Japan). High-sensitivity C-reactive protein, erythrocyte sedimentation rate, creatinine, blood urea nitrogen), glycaemia and complete blood picture were also recorded (Hitachi 747; Hitachi Ltd., Tokyo, Japan) (PARK J-W *et al*., 2002; KOBATA *et al.*, 2004).

Body composition

Body composition was measured using fan-beam dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy DXA; GE Medical Systems, Waukesha, WI, USA). The *in vivo* coefficients of variation were respectively 4.20% and 0.48% for fat and muscle mass. All measurements for each parameter were made by the same investigator. Total body fat mass was obtained with a whole body scan. A skeletal muscle index was calculated as the sum of the fat-free soft tissue mass of arms and legs (CRUZ-JENTOFT, 2013). Body weight was measured to the nearest 0.1 kg using a precision scale, with the subjects wearing light clothing and without shoes, using a standardized technique, and BMI was calculated (kg/m^2).

Statistical analysis

In order to analyze the effects of different endogenous and health factors (i.e. explanatory variables) on taste and smell perception and food preference factors returned by factor analysis (i.e. the outcome variables), we performed a multivariate multiple regression model (MRA) with R software (46) (v. 3.0.3: package lavaan v.0. 5.17: ROSSEEL, 2012).

RESULTS

Table 1 and table 2 show the baseline characteristics of the sample. We endrolled 272 women and 88 men with mean age of 72 years old.

In table 2 we assessed the prevalence genotype of polymorphisms. Low percentage of elderly subject was found in rs7903146 (TT= 15.8%) in rs35874116 (GG=15%), rs35744813 (TT=0.8%), rs2274333 (GG=7,5%), and rs307355 (TT=0,4%). Heterogygous genotype was higher in rs713598 in 50,9% and rs7903146 (CT: 49,2%) , in rs9939609 (AT: 51,1%); s35874116 (AG: 47,3%), rs2274333 (AA: 51,6%), rs7792845 (AG: 49,5%); rs35744813 (CC: 86,5%), rs307355 (CC 87,6%).

In overall the heterozygous genotype seems to be closed to higher risk of sarcopenia. As showed no statistically difference amoung genotipes is showed (exception for s35744813 heterozygous that seems to be associate with a better muscle health).

Table 1. Baseline characteristics of the sample.

Participants= 360 subjects	women= 272	Men= 88
age 65-70 = 55 subjects age 70-75 = 55 subjects age 75-80 = 65 subjects age 80-85 = 45 subjects age 85-90 = 53 subjects age 90 -95 = 42subjects age 95-100 = 44 subjects	72.1 2± 7.94	72.56 ± 5.41
BMI (kg\m2)	26.30 ± 5.50	27.74 ± 5.71
Appendicular Lean Mass Index	6.43 ± 1.80	8.274 ± 1.44

Table 2. Frequencies distribution of the genotypes in different gene polymorphysms.

Polymorphism and GENE	genotypes	%
rs713598 **TAS2r38 gene**	CC	24,2
	CG	50,9
	GG	24,8
rs7903146 **TCF7L2 Gene**	CC	35
	CT	49,2
	TT	15,8
rs9939609 FTO **gene**	AA	15,3
	AT	51,1
	TT	33,6
rs35874116 **TAS1R2 gene**	AA	37,6
	AG	47,3
	GG	15
rs2274333 (**CA6) gene**	AA	51,6
	AG	40,8
	GG	7,5
rs7792845 **GNAT3 gene**	AA	19,9
	AG	49,5
	GG	30,5
rs35744813 **TAS1R3 gene**	CC	86,5
	CT	12,7
	TT	0,8
rs307355 **TAS1R3 gene**	CC	87,6
	CT	12
	TT	0,4

Table 3. Risk of sarcopenia in heterozygous and homozygous genotype in comparison to reference.

RISK OF SARCOPENIA (SMI)	Reference value	heterozygous		homozygous	
POLIMORPHISM	B	B	P value	B	P value
s713598_GC	1 (1; 1)	-0.28 0	0,374	-0.195	0.476
s7903146_TC	1 (1; 1)	-0.260	0.307	-0.687	0.505
s9939609_TA	1 (1; 1)	0.381	0.256	0.373	0.294
s35874116_GA	1 (1; 1)	-0,233	0,346	-0,344	0,280
s2274333_GA	1 (1; 1)	0,094	0.678	0,123	0.803
s7792845_GA	1 (1; 1)	-0,215	0,484	-0,253	0.434
s35744813_TC	1 (1; 1)	0,800	p<0.05	0.965	0,537
s307355_TC	1 (1; 1) -	-1,112	0,488	-213	0.896

In figure 1 are showed *t*he bar charts of age by genotype of showing the association between the polymorphism of rs35874116 and TAS1R2 gene. The A/G genotype frequency is about 50% in all classes (65–100 years). The association between the polymorphism of rs9939609 in FTO gene shows that A/T genotype frequency is about 50% in all classes (65–100 years). Thereafter the T/T frequency increases continuously through older classes reaching the 80% in the oldest (p trend <0.001). The association between the polymorphism of rs7903146 and TCF7L2 Gene shows that the C/T genotype frequency is about 50% in all classes (65–100 years). The association between the polymorphism of rs713598 in TAS2r38 gene shows that the C/C genotype frequency is about 50% in all classes (65–95 years. Thereafter the G/G frequency decreases continuously through older classes reaching the 0% in (95-100) (p trend <NS). The association between the polymorphism of rs2274333 (CA6) gene show that the A/A genotype frequency is about 15% in all classes (65–95 years) but appears decrease in oldest old and reach zero (95-100). Thereafter the A/G frequency increases continuously through older classes reaching the 80% in (95-100) (p trend <0.05). The association between the polymorphism of rs7792845 (gnat3) gene. The A/A genotype frequency is about 15% in all classes (65–95 years) but appears decrease in oldest old and reach zero (95-100). The association between the polymorphism of rs35744813 TAS1R3 gene shows the C/C genotype frequency is about OVER 80% in all classes (65–95 years) but appears increase in oldest old and reach 100% (95-100) Thereafter the C/T and T frequency decrease continuously through older classes reaching the 0%in T/T and 5% in C/T in (95-100) (p trend <0.05). The association between the polymorphism of rs307355 TAS1R3 gene shows that C/C genotype frequency is about OVER 80.% in all classes (65–95 years).

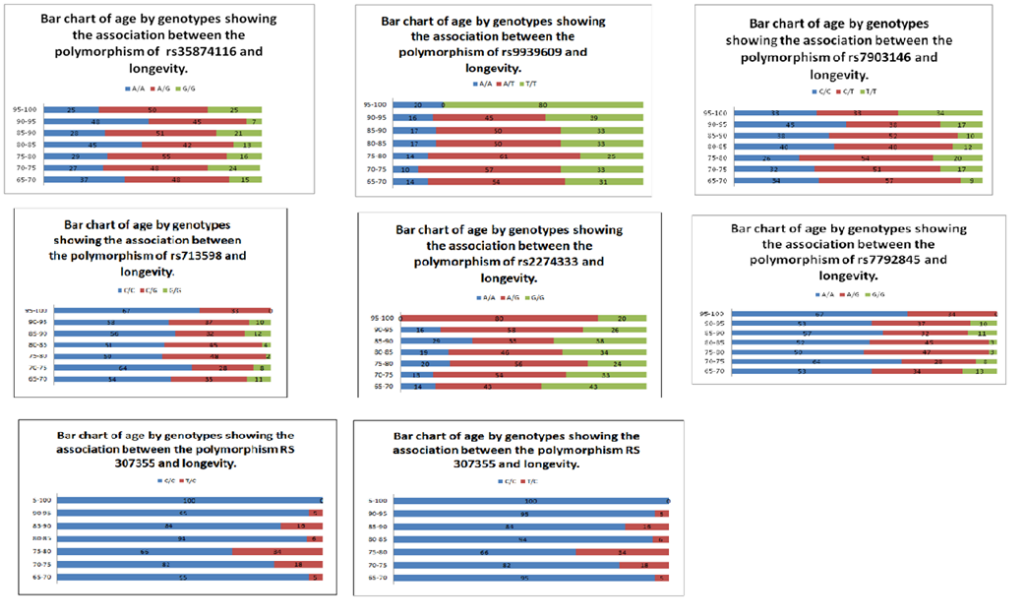

Figure 1. Trend for age and genotype distribution

DISSCUSION

In the present study, it has been investigated the possible associations between longevity and SNPs in 9 candidate genes. Our intensive SNP tagging approach along with the analyses of haplotypes provides a close to exhaustive analysis of the possible associations of longevity with the known common polymorphic variant. The first important descriptive point that emerged by this study is the low percentage of elderly subject that was found in rs7903146 (TT= 15.8%) in rs35874116 (GG=15%), rs35744813 (TT=0.8%) and in rs2274333 (GG=7.5%). Overall, this founding showed that the polymorphism rs9939609, of the FTO gene, shows an association with longevity. In particular, the frequency of T/T homozygotes increases gradually from 35% in subjects aged 65-80 ys up to 80% in centenarians. The polymorphism of rs2274333 (CA6) gene shows that A/G frequency increases continuously through older classes reaching the 80% in (95-100). Another important founding regards the polymorphism of rs35744813 of TAS1R3 gene. The C/C genotype frequency is over 80% in all classes (65–95 years) but appears increase in oldest old and reaches the 100% in (95-100 ys). While T allele frequency decrease continuously through older classes reaching the 0% in T/T and 5% in C/T in (95-100) (p-trend <0.05). These data provide suggestive evidence on the possible correlation between human longevity and FTO gene (obesity related), CA6 gene (the gustin- bitter taste related) and TAS1R3 (umami taste stimulus related).

As documented by this study the polymorphism of rs9939609 the FTO gene genotype T/T frequency increases continuously through older classes reaching the 80% in the oldest old. This is a confirmatory result because a recent finding shows that subjects with at least one A allele had significantly greater body mass indexes, body mass index, and fat mass consumed a greater percentage of energy from fat than did the TT subjects (TANOFSKY-KRAFF *et al*., 2009).

In this study the polymorphism of rs35744813 of TAS1R3 associated with longevity, we know that subject with T/T might cause the inability to taste the bitterness of phenylthiocarbamide (PTC) and similar molecules in foods (like cabbage and raw broccoli) or drinks (like coffee and dark beers).

On the other hand, similar molecules in foods would taste unpleasantly bitter to you instead of sweet. But this explanation is undocumented in literature and it is only an hypothesis. In other hand, it means that G/G explain a decrease of longevity.

A recent study states that responsiveness to PROP is inversely related to BMI and salivary ionic zinc concentrations in this gene. The gustin gene dimorphism rs2274333 observed in supertaster (A/A) and nontaster (G/G) subjects may influence the protein conformation and, thereby, affect zinc ion binding (PADIGLIA *et al.*, 2010).

This study, keep in light that the polymorphism of rs35744813 of TAS1R3 shows a decrease continuously through older classes with T allele.

A recent study on this gene has highlighted that, that sweet preference correlated with TAS1R3 genotype (MENNELLA *et al*., 2014).

Last but not least, this study takes in account the polymorphism of rs35744813 that explain a lower risk of relative muscle index and then a lowering risk on sarcopenia. In according the previous data on longevity, people with T are not able to detect bitter taste, and for this reason might affect the protein consumption and then improving muscle health and protein synthesis. As demonstrate recently the T allele results in reduced promoter activity in comparison to the C alleles, consistent with the phenotype observed in humans carrying T alleles and rs35744813 SNPs affect gene transcription by altering the function of this regulatory element and coding sequence strongly correlate with human taste sensitivity to sucrose, and this relationship can affect the insulin growth factor, a key point into the development of sarcopenia.

These data provide suggestive evidence on the possible correlation between human longevity and FTO gene (obesity related), CA6 gene (the gustin- bitter taste related) and TAS1R3 (umami taste stimulus related). No associations with sarcopenia were detected.

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DA LI SU GENI *CA6, TAS2R38, TCF7L2, FTO, TAS1R2, TAS1R3, GNAT3* RECEPTORI POLIMORFIZMA UKLJUČENI U IZUZETNU DUGOVEČNOST I RIZIK OD SARKOPENIJE?ISTRAŽIVANJE KOD STANOVNIŠTVA ITALIJE

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Izvod

Pretpostavili smo da genetski polimorfizmi različitih gena mogu da utiču na životni vek i zdravlje mišića ili sarkopeniju. Istražili smo moguće veze između dugovečnosti i uobičajenog polimorfizma genetskih varijacija, kao što su rs713598, rs7903146, rs9939609, rs35874116, rs2274333, rs7792845, rs35744813 u populaciji od 360 starijih Italijana u dobi od 65 do 100 godina. Polimorfizam rs9939609 gena FTO pokazuje povezanost (p <0,001) sa dugovečnošću. Konkretno, učestalost T/T homozigota postepeno raste od 35% kod ispitanika starih 65-80 godina do 80% u stogodišnjaka. Takođe polimorfizam gena rs2274333 (CA6) pokazuje da se A/G frekvencija kontinuirano povećava kroz starije klase dostižući 80% kod 95-100godina (p trend <0,05). Drugo važno otkriće tiče se polimorfizma rs35744813 gena TAS1R3. Učestalost C/C genotipa je preko 80% u svim klasama (65–95 godina), ali izgleda da se povećava kod najstarijih i dostiže 100% (95–100 godina). Dok se frekvencija alela T kontinuirano smanjuje kroz starije razrede dostižući 0% u T/T i 5% u C/T u (95-100) (p-trend <0,05). Ovi podaci ukazuju na moguću povezanost dugovečnosti i FTO gena (povezanog sa gojaznošću), gena CA6 (gustin-povezanog sa gorkim ukusom) i TAS1R3 (umami- povezanog sa stimulusom ukusa). Asocijacija sa sarkopenijom niije utvrđena.

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