Annals of Human Biology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iahb20

GSTT1, *GSTP1* and *XPC* genes are associated with longevity in an Italian cohort

Manuel Scarfò, Chiara Sciandra, Stefano Ruberto & Alfredo Santovito

To cite this article: Manuel Scarfò, Chiara Sciandra, Stefano Ruberto & Alfredo Santovito (2021): *GSTT1*, *GSTP1* and *XPC* genes are associated with longevity in an Italian cohort, Annals of Human Biology, DOI: 10.1080/03014460.2021.1985170

To link to this article: https://doi.org/10.1080/03014460.2021.1985170

ANNALS OF HUMAN BIOLOGY
https://doi.org/10.1080/03014460.2021.1985170

SHORT REPORT

GSTT1, *GSTP1* and *XPC* genes are associated with longevity in an Italian cohort

Manuel Scarfò, Chiara Sciandra, Stefano Ruberto and Alfredo Santovito

Department of Life Sciences and Systems Biology, University of Turin, Torino, Italy

ABSTRACT

Longevity is a complex process controlled by environmental and genetic factors. We evaluated the association of seven drug metabolising and DNA-repair gene polymorphisms with longevity in an Italian cohort. A sample of 756 subjects aged 18-98 was genotyped for *CYP1A1* (rs1048943, A>G), *GSTM1* (rs 1183423000, presence/absence), *GSTT1* (rs1601993659, presence/absence), *GSTP1* (rs1695, A>G), *XRCC1* (rs1799782, C>T), *XRCC1* (rs25489, A>G) and *XPC* (rs2228001, A>C) gene polymorphisms. The association between the studied gene polymorphisms and longevity was evaluated by dividing the sample into three age groups: 18–50, 51–85, and 86–98. We observed a significant decrease in the frequency of the *GSTT1* null, *GSTP1* G and *XPC* C alleles in the oldest group with respect to the youngest one. We also obtained the same results when dividing the sample into 18–85 and 86–98 age groups. The general linear model analyses confirmed a significant decreasing trend with age of the above mentioned alleles. We hypothesised that these minor alleles, being important in the sensitivity against the development of different types of cancer, may reflect a reduced life-expectancy in carrier subjects and may explain their significantly lower frequency observed among subjects belonging to the oldest age group.

ARTICLE HISTORY
Received 30 December 2020
Revised 24 August 2021
Accepted 25 August 2021

KEYWORDS
Aging; glutathione S-transferases; cytochrome P450; DNA-repair; metabolic genes

1. Introduction

Longevity is a complex trait controlled by both environmental and genetic factors. Most of the published papers about the genetic basis of longevity are principally focussed on those gene polymorphisms related to susceptibility to cardiovascular diseases, such as *FTO*, *ACE* and *ApoE* (Santovito et al. 2019), while the relationship between drug metabolising and DNA-repair gene polymorphisms and longevity has been poorly studied (Debrabant et al. 2014; Dato et al. 2018; Kim et al. 2018).

Drug metabolising enzymes (DMEs) are involved in the metabolism and elimination of xenobiotic compounds to which humans are exposed, and include phase I and phase II metabolising enzymes and phase III transporter enzymes (Xu and Wei 2015). The first two classes of enzymes allow the biotransformation of lipid-soluble xenobiotic compounds into a more hydrophilic metabolite through oxidation reactions (phase I cytochrome P450 (CYP) superfamily enzymes) and conjugation reactions (phase II glutathione S-transferases (GST) enzymes) (Wauthier et al. 2007; Xu and Wei 2015). At the end of the process, phase III transporters help in transferring the more hydrophilic products outside the cells (Almazroo et al. 2017).

In order to prevent the deleterious consequences of mutagenic processes induced by environmental xenobiotics, cells evolved different mechanisms of DNA repair, depending on the specific type of DNA damage. DNA-repair genes, being responsible for maintaining the integrity of the genome, may be considered as longevity-associated genes and the fact that a reduced repair capacity has been reported to be associated with cancer development should also be considered (Langie et al. 2015).

Given these premises, in the present study we decided to evaluate both the frequencies of seven polymorphic drug metabolising and DNA-repair genes and the variation of these frequencies in different age groups in a sample of a Northern Italian population. We considered the following most studied cancer-associated gene polymorphisms: *CYP1A1* (rs1048943), *GSTM1* (rs1183423000), *GSTT1* (rs1601993659), *GSTP1* (rs1695), X-ray repair cross-complementing group 1 (*XRCC1*) (rs1799782 and rs25489) and Xeroderma pigmentosum complementation group C (*XPC*) (rs2228001).

The *CYP1A1* gene is highly polymorphic and plays a central role in the metabolism of polycyclic aromatic hydrocarbons (Androutsopoulos et al. 2009). In this study we considered the *CYP1A1* rs1048943 single nucleotide polymorphism (SNP) in which adenine is replaced by guanine, resulting in the amino acid substitution Ile(462)Val (Wei and Hu 2015).

GST genes codify for one of the major groups of phase II detoxifying enzymes, evolved to protect organisms against toxic substances (Nebert and Vasiliou 2004). The polymorphisms of *GSTM1* and *GSTT1* genes consist of a deletion of a segment of DNA, with the subsequent lack of protein synthesis in homozygous individuals (Nebert and Vasiliou 2004).

CONTACT Alfredo Santovito alfredo.santovito@unito.it Department of Life Sciences and Systems Biology, University of Turin, Via Accademia Albertina n. 13, Torino 10123, Italy.

Supplemental data for this article is available online at https://doi.org/10.1080/03014460.2021.1985170.

Table 1. Allele and Genotype Frequencies of seven gene polymorphisms in an Italian sample ($n = 756$).

Gene polymorphisms	Allele	*N*	Frequency	Genotype	*N*	Frequency	HWE *p* Value
CYP1A1 (rs1048943)	A	1274	0.843	AA	**543**	0.718	0.305
	G	238	0.157	AG	**188**	0.249	
				GG	**25**	0.033	
GSTM1 (rs1183423000)	+	1054	0.697	+	**527**	0.697	Not done
	−	458	0.303	−	**229**	0.303	
GSTT1 (rs1601993659)	+	1088	0.720	+	**544**	0.720	Not done
	−	424	0.280	−	**212**	0.280	
GSTP1 (rs1695)	A	1267	0.838	AA	**537**	0.710	0.193
	G	245	0.162	AG	**193**	0.255	
				GG	**26**	0.035	
XRCC1 (rs1799782)	C	1294	0.856	CC	**559**	0.739	0.215
	T	218	0.144	CT	**176**	0.233	
				TT	**21**	0.028	
XRCC1 (rs25489)	A	1331	0.880	AA	**591**	0.782	0.204
	G	181	0.120	AG	**149**	0.197	
				GG	**16**	0.021	
XPC (rs2228001)	A	1286	0.851	AA	**553**	0.731	0.217
	C	226	0.149	AC	**180**	0.238	
				CC	**23**	0.031	

HWE: Hardy-Weinberg Equilibrium (X^2-test).
Not done: the HWE was not calculated because the used genotyping procedure does not consent to discriminate the heterozygotes from homozygotes.

GSTP1 is the major isoenzyme expressed in human lung tissue. The SNP changes an adenine with a guanine in codon 105, resulting in the replacement of an isoleucine with a valine in the enzyme (López-Cima et al. 2012).

The *XRCC1* gene, involved in the Base Excision Repair (BER) pathway, encodes enzymes having an important role in the repair of single-strand DNA breaks associated with exposure to free oxygen radicals, radiation, ultraviolet, and alkylating agents (Caldecott 2019). In the present study, we evaluated the frequencies of the two most common SNPs, rs1799782 and rs25489.

Finally, an important key gene belonging to the Nucleotide Excision Repair (NER) pathway is XPC encoding a 940 amino-acid protein involved in DNA damage recognition and apoptosis (Fontana et al. 2008). We analysed one of the most common polymorphisms of this gene, represented by A>C transition in exon 15 (rs2228001), resulting in a lysine-to-glutamine substitution at position 939 (Fontana et al. 2008).

Given the above-mentioned role of metabolic and DNA-repair gene polymorphisms in the modulation of genomic damage and in the maintenance of DNA integrity, the aim of this work was to evaluate the possible role of these gene polymorphisms in longevity. The hypothesis was that some variants of these genes, being associated with a different efficiency in both metabolising potentially harmful environmental xenobiotics and in repairing genomic damage, may be differentially represented in elderly individuals, giving them an advantage or a disadvantage in terms of longevity.

2. Subjects and methods

2.1. Subjects

We recruited healthy subjects (persons not hospitalised on the date of the sampling and without familiar history of genetic pathologies), who were natives of Piedmont localities for at least two generations, and voluntarily joined the project. In order to avoid selection bias, subjects were sampled without *a priori* exclusions, for example in terms of age and sex. The nutritional status was evaluated by the body mass index (BMI). Since obesity is considered as a pathological status (Lu et al. 2018), we excluded obese subjects from the sampling (subjects with BMI $\geq$ 30 Kg/m^2).

All data from each participant, including ancestry, were collected during an interview in an open-ended manner. We excluded the subjects who claimed to be natives of other Italian regions or who belonged to religious ethnic groups. All subjects received detailed information about the study and gave their written informed consent. Personal data were collected in an anonymous manner and participants were informed about their right to privacy and about the management procedures of their personal data.

In order to evaluate the possible association of some alleles with longevity, we decided to divide our sample into three age groups: 18–50, 51–85, and 86–98, representing individuals in reproductive, post-reproductive and long-lived phases, respectively (Santovito et al. 2019). The study was conducted with the formal approval of the Bioethical Committee of the University of Turin ethical committee and was performed in accordance with the ethical standards laid down in the 2013 Declaration of Helsinki.

2.2. DNA Extraction and genotyping

Blood collection, DNA extraction and PCR reactions were performed according to the protocol described in Santovito et al. (2017). We analysed the following gene polymorphisms: *CYP1A1* (rs1048943, A>G), *GSTM1* (rs 1183423000, presence/absence), *GSTT1* (rs1601993659, presence/absence), *GSTP1* (rs1695, A>G), *XRCC1* (rs1799782, C>T), *XRCC1* (rs25489, A>G) and *XPC* (rs2228001, A>C). Primer sequences, annealing temperatures, PCR methodologies and expected PCR product sizes are reported in Supplementary Material 1.

2.3. Statistical analysis

All statistical analyses were performed using the SPSS software statistical program (version 25.0, SPSS Inc., Chicago, USA). Pearson's $\chi 2$ test contingency table was used to evaluate the Hardy-Weinberg equilibrium (HWE), whereas comparison of genotype frequencies between age groups was carried out using the Fisher's exact test. The correlation between age and a specific genotype was analysed using a multivariate general linear model with Bonferroni's correction. All p values were two-tailed, and the level of statistical significance was set at $p < 0.05$ for all tests.

3. Results

We recruited 756 subjects (mean age ± SD: 55.88 ± 22.68), including 335 males (mean age ± SD: 47.499 ± 17.65) and 421 females (mean age ± SD: 46.08 ± 21.62). The 18–50 age group comprised 538 subjects (mean age ± SD: 35.80 ± 7.80), whereas the 51–85 age group included 151 subjects (mean age ± SD: 66.42 ± 11.57) and 67 subjects (mean age ± SD: 89.87 ± 2.64) belonged to the 86–98 age group.

Allele and genotype frequencies are reported in Table 1. All gene polymorphisms were in HWE. The frequencies of the studied gene polymorphisms among age groups are shown in Table 2.

We observed a significant decrease in the frequency of *GSTT1* null, *GSTP1* G and *XPC* C alleles in the oldest group with respect to the youngest one ($p = 3.72 \times 10^{-2}$, $p = 1 \times 10^{-4}$ and $p = 4.2 \times 10^{-3}$, respectively) and with respect to the 51–85 age group ($p = 8 \times 10^{-4}$, $p = 1 \times 10^{-4}$ and $p = 5.9 \times 10^{-3}$, respectively). For *GSTT1* null and *GSTP1* G alleles significant differences were also found between age groups 51–85 and 18–50 ($p = 2 \times 10^{-2}$ and $p = 5.7 \times 10^{-3}$,

Table 2. Frequencies of the studied metabolic gene polymorphisms among different age groups ($n = 756$).

Gene Variants	18–50 $N = 538$	51–85 $N = 151$	86–98 $N = 67$	18–85 $N = 689$	86–98 $N = 67$
CYP1A1 (rs1048943)					
AA	389	106	48	495	48
AG	128	41	19	169	19
GG	21	4	0	25	0
Allele A	906 (0.842)	253 (0.838)	115 (0.858)	1159 (0.841)	115 (0.858)
Allele G	170 (0.158)	49 (0.162)	19 (0.142)	219 (0.159)	19 (0.142)
GSTM1 (rs1183423000)					
+	378 (0.703)	97 (0.642)	52 (0.176)	475 (0.689)	52 (0.776)
−	160 (0.297)	54 (0.358)	15 (0.224)	214 (0.311)	15 (0.224)
GSTT1 (rs1601993659)					
+	392 (0.729)	95 (0.629)	57 (0.851)	487 (0.707)	57 (0.851)
−	146 (0.271)	56 (0.371)[a]	10 (0.149)[b,c]	202 (0.293)	10 (0.149)[d]
GSTP1 (rs1695)					
AA	360	117	60	477	60
AG	154	32	7	186	7
GG	24	2	0	26	0
Allele A	874 (0.812)	266 (0.881)	127 (0.948)	1140 (0.827)	127 (0.948)
Allele G	202 (0.188)	36 (0.119)[e]	7 (0.052)[f,g]	238 (0.173)	7 (0.052)[h]
XRCC1 (rs1799782)					
CC	395	109	55	504	55
CT	128	36	12	164	12
TT	15	6	0	21	0
Allele C	918 (0.853)	254 (0.841)	122 (0.910)	1172 (0.851)	122 (0.910)
Allele T	158 (0.147)	48 (0.159)	12 (0.090)	206 (0.149)	12 (0.090)
XRCC1 (rs25489)					
AA	430	110	52	539	52
AG	97	36	15	134	15
GG	11	5	0	16	0
Allele A	957 (0.889)	256 (0.848)	119 (0.888)	1213 (0.880)	119 (0.888)
Allele G	119 (0.111)	46 (0.152)	15 (0.112)	165 (0.120)	15 (0.112)
XPC (rs2228001)					
AA	389	106	58	495	58
AC	130	41	9	171	9
CC	19	4	0	23	0
Allele A	908 (0.844)	253 (0.838)	125 (0.933)	1161 (0.843)	125 (0.933)
Allele C	168 (0.156)	49 (0.162)	9 (0.067)[i,j]	217 (0.157)	9 (0.067)[k]

[a] $P = 2 \times 1\ 0^{-2}$ significant with respect to 18–50 age group.
[b] $P = 3.72 \times 1\ 0^{-2}$ significant with respect to 18–50 age group.
[c] $P = 8 \times 1\ 0^{-4}$ significant with respect to 51–85 age group.
[d] $P = 1.05 \times 1\ 0^{-2}$ significant with respect to 18–85 age group.
[e] $P = 5.7 \times 1\ 0^{-3}$ significant with respect to 18–50 age group.
[f] $P = 1.0 \times 1\ 0^{-4}$ significant with respect to 18–50 age group.
[g] $P = 3.58 \times 1\ 0^{-2}$ significant with respect to 51–85 age group.
[h] $P = 1.0 \times 1\ 0^{-4}$ significant with respect to 18–85 age group.
[i] $P = 4.2 \times 1\ 0^{-3}$ significant with respect to 18–50 age group.
[j] $P = 5.9 \times 1\ 0^{-3}$ significant with respect to 51–85 age group.
[k] $P = 3.4 \times 1\ 0^{-3}$ significant with respect to 18–85 age group.

respectively). For the other studied gene polymorphisms, no significant differences were found between the different age groups.

The sample was also subdivided into two age groups, 18–85 and 86–98, and we obtained the same results, with the oldest age group showing a significant decrease of the *GSTT1* null ($p = 1.05 \times 10^{-2}$), *GSTP1* G ($p = 1 \times 10^{-4}$) and *XPC* C ($p = 3.4 \times 10^{-3}$) allele frequencies with respect to the 18–85 age group.

Finally, the multivariate general linear model confirmed this significantly decreasing trend with age for the *GSTT1* null ($p = 3.2 \times 10^{-2}$), *GSTP1* G ($p = 8 \times 10^{-3}$) and *XPC* C ($p = 3.4 \times 10^{-2}$) alleles.

4. Discussion

Although longevity is due to a complex interaction of genetic and environmental factors, a strong genetic component appears to have an important role in survival to extreme ages (Franceschi et al., 2020; Brooks-Wilson, 2013; Gems and Partridge 2013).

In the present paper we found a negative association of *GSTT1* rs1601993659 null, *GSTP1* rs1695 *G* and *XPC* rs2228001 C alleles with human longevity in an Italian sample. A possible explanation for our findings is that polymorphisms of the metabolic and DNA-repair genes could play an important role in determining the incidence of diseases associated with genomic damage and, consequently, in modulating the life span. For example, many studies have shown that variants of *GSTs* genes are significantly associated with disease risk, including cancer, cardiovascular and allergic diseases (Di Pietro et al. 2010; Esalmi and Sahebrak 2014; Dar et al. 2017). The lowest frequency of *GSTT1* null genotypes found in subjects aged between 86 and 98 years seems to suggest a selective disadvantage of the possible detrimental genotypes in this age group.

Vice versa, this association with longevity was not observed for *GSTM1* polymorphism. This result is not surprising and agrees with what other authors have observed. For example, a lack of association between human longevity and *GSTM1* gene polymorphism was already observed by Muiras et al. (1998). Similarly, Ruiz et al. (2012), in a Spanish sample, observed a significantly higher frequency for the *GSTT1*-positive allele in a sample of centenarians (age range 100–108) than in a control group (age range 19–43), while the frequency of the *GSTM1*-positive allele was similar in both groups.

Differently to *GSTT1* and *GSTM1* gene polymorphisms, no data are present in the literature about the relationships between *GSTP1* rs1695 (A>G) gene polymorphism and longevity. However, like *GSTT1*, *GSTP1* also has a corresponding rationale for an association with age. In subjects carrying the variant G-allele, substrate-specific catalytic activity becomes less effective, resulting in increased risk for the development of chronic and malignant diseases, such as cardiovascular diseases and neoplasms (Khabaz 2014; Chielle et al. 2016)' and, consequently, in a reduced longevity.

In the literature a relationship between *CYP1A1* variants and cancer was observed (Liu et al. 2016), however we found no differences between age groups in the frequency of *CYP1A1* rs1048943 genotypes. These data seem to be concordant with other studies, such as the one conducted by Taioli et al. (2001), that did not find any difference in the frequency of *CYP1A1* alleles in centenarians, as compared to younger control subjects. However, published data evaluating the possible association between phase I enzyme polymorphisms and ageing reported conflicting results (Wauthier et al. 2007; Seripa et al. 2010).

Several investigations have demonstrated that subjects showing compromised repair capacity have increased mutation rates, an increased risk of cancer and a reduced life-expectancy (Tian et al. 2017; Kim et al. 2018). We hypothesised that polymorphisms in the *XPC* gene, being important in the sensitivity against the development of different types of cancer (Bahceci et al. 2015), may reflect a reduced life-expectancy in carrier subjects and may explain the significant lower frequency of *XPC* exon 15 C-allele we observed among subjects belonging to oldest age group.

Conversely, there is no consensus regarding the possible association between *XRCC1* rs1799782 and rs2228001 polymorphisms with different types of cancer (Moghaddam et al. 2016; Dylawerska et al. 2017), data that may explain the lack of association of these gene polymorphisms with longevity, as observed in our study.

In conclusion, with this study we highlighted a role for *GSTT1*, *GSTP1* and *XPC* gene polymorphisms in longevity. We hypothesised that the minor alleles of these metabolic genes, playing an important role in the susceptibility to different types of cancer, may reflect a reduced life-expectancy in carriers, explaining their significantly lower frequency observed among subjects belonging to the oldest age group. Conversely, an optimum activity of repair processes may favour longevity, justifying the significant reduced frequency of *XPC* C allele in elderly subjects.

Finally, we would like to emphasise that, considering that the number of centenarians in the world will drastically increase in the next few decades (Nijiati et al. 2013), studies on longevity will play an important role, and will also allow us to analyse any pleiotropic effects of analysed genes.

Informed consent

Written informed consent was obtained from all subjects involved in the study. Participants were also informed about their right to privacy and about the management procedures of their personal data, as required by the Italian law (art. 13 of Legislative Decree n. 196/2003).

Author contributions

Manuel Scarfò, Chiara Sciandra and Stefano Ruberto extracted DNA, performed genotyping and drafted manuscript. Alfredo Santovito designed the project, collected the samples, performed genotyping, drafted and edited the manuscript.

Disclosure statement

The Authors declare that they have no competing financial interests in relation to the present work.

Funding

This study was supported by University of Turin with local 2015-2018 grants.

ORCID

Alfredo Santovito http://orcid.org/0000-0001-5292-5206

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Almazroo OA, Miah KM, Venkataramanan R. 2017. Drug metabolism in the liver. Clin Liver Dis. 21(1):1–20.

Androutsopoulos VP, Tsatsakis AM, Spandidos DA. 2009. Cytochrome P450 CYP1A1: wider roles in cancer progression and prevention. BMC Cancer. 9(9):187.

Bahceci A, Paydas S, Tanriverdi K, Ergin M, Seydaoglu G, Ucar G. 2015. DNA repair gene polymorphisms in B cell non-Hodgkin's lymphoma. Tumour Biol. 36(3):2155–2161.

Brooks-Wilson AR. 2013. Genetics of healthy aging and longevity. Hum Genet. 132(12):1323–1338.

Caldecott KW. 2019. XRCC1 protein; Form and function. DNA Repair. 81: 102664.

Chielle EO, Fortuna PC, Maziero JS. 2016. Association between the glutathione S-transferase P1 (GSTP1) Ile105Val gene polymorphism in obese and overweight patients over 60 years. J Bras Patol Med Lab. 52:211–216.

Dar A, Faryal R, Masood N. 2017. Possible association of a distinct combined Glutathione-S-transferase members with allergic asthma patients in Pakistan. Genes Dis. 4(2):111–115.

Dato S, Soerensen M, De Rango F, Rose G, Christensen K, Christiansen L, Passarino G. 2018. The genetic component of human longevity: new insights from the analysis of pathway-based SNP-SNP interactions. Aging Cell. 17(3):e12755.

Debrabant B, Soerensen M, Flachsbart F, Dato S, Mengel-From J, Stevnsner T, Bohr VA, et al. 2014. Human longevity and variation in DNA damage response and repair: study of the contribution of sub-processes using competitive gene-set analysis. Eur J Hum Genet. 22(9):1131–6113.

Di Pietro G, Magno LAV, Rios-Santos F. 2010. Glutathione S-transferases: an overview in cancer research. Expert Opin Drug Metab Toxicol. 6(2): 153–170.

Dylawerska A, Barczak W, Wegner A, Golusinski W, Suchorska WM. 2017. Association of DNA repair genes polymorphisms and mutations with increased risk of head and neck cancer: a review. Med Oncol. 34(12): 197.

Esalmi S, Sahebrak A. 2014. Glutathione-S-transferase M1 and T1 null genotypes are associated with hypertension risk: a systematic review and meta-analysis of 12 studies. Curr. Hypertens. Res. 16(6):432.

Fontana L, Bosviel R, Delort L, Guy L, Chalabi N, Kwiatkowski F. 2008. DNA repair gene ERCC2, XPC, XRCC1, XRCC3 polymorphisms and associations with bladder cancer risk in a French cohort. Anticancer Res. 28(3B):1853–1856.

Franceschi C, Garagnani P, Olivieri F, Salvioli S, Giuliani C. 2020. The contextualized genetics of human longevity: JACC focus seminar. J Am Coll Cardiol. 75(8):968–979.

Gems D, Partridge L. 2013. Genetics of longevity in model organisms: debates and paradigm shifts. Annu Rev Physiol. 75:621–644.

Hu Z, Wang Y, Wang X, Liang G, Miao X, Xu Y, Tan W, Wei Q, et al. 2005. DNA repair gene XPC genotypes/haplotypes and risk of lung cancer in a Chinese population. Int J Cancer. 115(3):478–483.

Khabaz MN. 2014. Polymorphism of the glutathione S-transferase P1 gene (GST-pi) in breast carcinoma. Pol J Pathol. 65(2):141–146.

Kim YJK, Kim HS, Seo YR. 2018. Genomic approach to understand the association of DNA repair with longevity and healthy aging using genomic databases of oldest-old population. Oxid Med Cell Longev. 2018:2984730.

Langie SAS, Koppen G, Desaulniers D, Al-Mulla F, Al-Temaimi R, Amedei A, Azqueta A, et al. 2015. Causes of genome instability: the effect of low dose chemical exposures in modern society. CARCIN. 36(Suppl 1): S61–S88.

Liu HX, Li J, Ye BG. 2016. Correlation between gene polymorphisms of CYP1A1, GSTP1, ERCC2, XRCC1, and XRCC3 and susceptibility to lung cancer. Genet Mol Res. 15(4):gmr15048813.

López-Cima MF, Álvarez-Avellón SM, Pascual T, Fernández-Somoano A, Tardón A. 2012. Genetic polymorphisms in CYP1A1, GSTM1, GSTP1 and GSTT1 metabolic genes and risk of lung cancer in Asturias. BMC Cancer. 12:433.

Lu DY, Che JY, Lu TR, Lu Y, Huang YK, Lu TL, Chen YZ, et al. 2018. Pathology and treatments of obesity. Trends Med. 18(5):1–2.

Moghaddam AS, Nazarzadeh M, Nooroozi R, Darvish H, Jarrahi AM. 2016. XRCC1 and OGG1 gene polymorphisms and breast cancer: a systematic review of literature. Iran J Cancer. 9(1):e3467.

Muiras ML, Verasdonck PV, Cottet F, Schächter F. 1998. Lack of association between human longevity and genetic polymorphisms in drug-metabolizing enzymes at the NAT2, GSTM1 and CYP2D6 loci. Hum Genet. 102(5):526–532.

Nebert DW, Vasiliou V. 2004. Analysis of the glutathione S-transferase (GST) gene family. Hum Genomics. 1(6):460–464.

Nijiati M, Saidaming A, Qiao J, Cheng Z, Qiu C, Sun Y. 2013. GNB3, eNOS, and mitochondrial DNA polymorphisms correlate to natural longevity in a xinjiang uygur population. PLoS One. 8(12):e81806.

Ruiz JR, Fiuza-Luces C, Buxens A, Cano-Nieto A, Gómez-Gallego F, Santiago C, Rodríguez-Romo G, et al. 2012. Are centenarians genetically predisposed to lower disease risk? Age. 34(5):1269–1283.

Santovito A, Gendusa C, Matini A, Ferraro F, Musso I, Costanzo M, Delclos A, Cervella P. 2017. Frequency distribution of six cytokine gene polymorphisms in North- and South-Italy. Int J Immunogenet. 44(4):158–163.

Santovito A, Galli G, Ruberto S. 2019. Evaluation of the possible association of body mass index and four metabolic gene polymorphisms with longevity in an Italian cohort: a role for APOE, eNOS and FTO gene polymorphisms. Ann Hum Biol. 46(5):425–429.

Seripa D, Pilotto A, Panza F, Matera MG, Pilotto A. 2010. Pharmacogenetics of cytochrome P450 (CYP) in the elderly. Ageing Res Rev. 9(4):457–474.

Taioli E, Mari D, Franceschi C, Bonafè M, Monti D, Bertolini S, Marinelli D, Garte S. 2001. Polymorphisms of Drug-Metabolizing Enzymes in Healthy Nonagenarians and Centenarians: Difference at GSTT1 Locus. Biochem Biophys Res Commun. 280(5):1389–1392.

Tian X, Seluanov A, Gorbunova V. 2017. Molecular mechanisms determining lifespan in short- and long-lived species. Trends Endocrinol Metab. 28(10):722–734.

Wauthier V, Verbeeck RK, Calderon PB. 2007. The effect of ageing on cytochrome p450 enzymes: consequences for drug biotransformation in the elderly. Curr Med Chem. 14(7):745–757.

Wei XP, Hu J. 2015. Cytochrome P450 1A1 exon 7 polymorphism and susceptibility to lung cancer in the Chinese population: an updated meta-analysis and review. Onco Targets Ther. 8: 1611–1618.

Xu L, Wei H. 2015. Association between CYP1A1 2454A>G polymorphism and colorectal cancer risk: a meta-analysis. J Can Res Ther. 11(4): 760–764.