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1 **Special article**

2 **The influence of nutrigenetics on biomarkers of selenium nutritional status**

3

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9

10 **Abstract**

11 Selenium (Se) is an essential micronutrient for human biology that executes its
12 functions as the amino acid selenocysteine via selenoproteins, which have important
13 functions, such as, antioxidant, immunomodulatory, thyroid metabolism and human
14 fertility. Se nutritional status is assessed using the quantification of blood Se
15 biomarkers influenced by several factors, including diet, age, gender, smoking status,
16 alcohol consumption, health condition and genetic characteristics of individuals.
17 Nutrigenetic studies have identified single nucleotide polymorphisms (SNPs) in

18 selenoproteins that might clarify the high variability in values reported for biomarkers
19 of Se nutritional status in different populations and the response of these biomarkers
20 to Se supplementation with either organic or inorganic forms of Se. This review aims
21 to (1) define the basic aspects of Se biology, (2) describe the current most commonly
22 used biomarkers of Se nutritional status and, (3) provide a state of the art of
23 associations observed between functional SNPs in selenoproteins and biomarkers of
24 Se status in healthy populations.

25

26 **Keywords:** single nucleotide polymorphisms, selenoproteins, glutathione peroxidase,
27 selenoprotein P.

28

29 **INTRODUCTION**

30 The essentiality of the trace element selenium (Se) to human health was first
31 reported in 1978 when its presence was discovered in the antioxidant erythrocyte
32 enzyme glutathione peroxidase.¹ Previous reviews on this topic have described this
33 discovery in detail.²⁻⁴ After recognizing its important functions for human health,
34 several studies have aimed to monitor the Se nutritional status of populations
35 worldwide.^{3,5,6} However, the controversial data of epidemiological and intervention
36 studies have demonstrated not only differences in the Se intake of populations from
37 different regions, but also different individual responses. In this context, the influence
38 of genetic variations in genes related to Se metabolism must be considered to
39 understand this scenario.⁷

40 Following the conclusion of the Human Genome Project (HGP) and the
41 advances in technology, numerous genetic variations in the human DNA sequence

42 have been described.⁸ Concerning Se metabolism, the identification of several
43 functional single nucleotide polymorphisms (SNPs) in selenoproteins has raised the
44 hypothesis that these SNPs could modify the biomarkers of Se status and modulate
45 its beneficial effect on the development of chronic diseases.⁷ In this context, the
46 nutrigenetic research field provides a better understanding of selenoprotein
47 metabolism and its biological function in humans, which could help researchers to
48 understand the data on Se status in different populations and the variable
49 interindividual response to Se dietary interventions. Investigating how the presence
50 of SNPs in selenoprotein genes modifies the biomarkers of Se status is crucial for a
51 better assessment of Se nutritional status and a future revision of Se dietary
52 recommendations according to the genetic characteristics of different populations or
53 individuals.

54 This review aims to (1) define the basic aspects of Se metabolism, function,
55 food sources, and nutritional recommendations; (2) describe the current most
56 commonly used biomarkers of Se nutritional status; and (3) provide a state of the art
57 of associations observed between functional SNPs in selenoproteins and biomarkers
58 of Se nutritional status in healthy populations.

59

60 **METHODS**

61 The search for articles was conducted using the PubMed database available
62 at www.ncbi.nlm.nih.gov/pubmed, and the terms “selenium”, “nutrigenetics” and the
63 specific SNPs “pro198leu,” “rs1050450,” “rs713041,” “rs3877899,” “rs7579,” “rs5845,”
64 and “rs34713741.” These SNPs were selected based on the literature search. The
65 inclusion criteria were as follows: studies conducted with healthy populations, both
66 genders or only males or females, an evaluation of one or more SNPs in

67 selenoprotein genes, and a quantification of biomarkers of Se nutritional status. The
68 studies included were observational, longitudinal, and randomized clinical trials.
69 Those conducted with a population with chronic diseases such as cancer,
70 cardiovascular disease, and diabetes and without the quantification of biomarkers of
71 Se nutritional status were excluded.

72

73 **BASIC ASPECTS OF SE BIOLOGY: FUNCTION, FOOD SOURCES, AND** 74 **DIETARY RECOMMENDATIONS**

75 Se is an essential trace element for human health with its biological role
76 directly related to the functions of selenoproteins and Se metabolites. Unlike other
77 minerals that interact with proteins as cofactors, Se is inserted into mammalian
78 selenoproteins as the 21st amino acid, selenocysteine (Sec). In mammals, 25
79 selenoprotein genes have been identified, while only half of them have been
80 functionally characterized.^{9,10} Sec is generally located in the active site of the
81 enzymes by using a mechanism that involves the recoding of the stop codon UGA
82 during translation. The incorporation of Sec into proteins occurs in the 3'UTR in the
83 Sec incorporation sequence (SECIS) region.¹¹ Most selenoproteins are involved in
84 biological processes that concern the control of the redox state and antioxidant
85 function.^{10,12}

86 One of the well established functions of selenoproteins is the redox activity
87 mainly attributed to five members of the glutathione peroxidase (GPx) family and
88 three isoforms of thioredoxin reductases (TXNRD) and deiodinases (DIO). They act
89 in the reduction of hydrogen peroxide (H₂O₂) and phospholipid hydroperoxides,
90 decreasing the overall oxidative damage to cell membranes, biomolecules, DNA, and
91 mitochondria.¹⁰ Se is also important for modulating the inflammatory response since

92 it attenuates the activation of the nuclear factor (NF)-kB pathway;^{13,14} protection
93 against toxic heavy metals, such as mercury and methyl mercury,¹⁵ and thyroid
94 function due to the action of deiodinases in the conversion of T₄ into its active form
95 T₃.^{16,17} Moreover, Se is critical for neurological function as it protects the brain
96 against oxidative damage,^{18,19} as well as male fertility and reproduction through the
97 role of GPX4 as an antioxidant in the early phase of spermatogenesis, which
98 guarantees the functional and structural integrity of spermatozoa.^{20,21} In the later
99 phase, GPX4 located in the mitochondria is essential to the sperm capsule
100 formation²¹.

101 In foods, Se can be presented as either organic (Sec and selenomethionine
102 [SeMet], Se- methyl-selenocysteine [SeMCys], and γ -glutamyl-Se-methyl-
103 selenocysteine) or inorganic forms (selenate). The inorganic form selenite is found in
104 supplements. In a normal physiological condition with an adequate intake, most
105 organic and inorganic forms are well absorbed (~70 - 90%), except for selenite,
106 which has an absorption no greater than 60%.⁴ Se concentration in foods varies
107 worldwide according to Se content and bioavailability in the soil and the capacity of
108 plants to accumulate Se.^{22,23} This geographical pattern of variation has a direct
109 impact on the Se nutritional status of global populations, with the lowest values found
110 in Eastern Europe, and the highest in Venezuela, the United States and Canada.
111 China has regions of deficiency and toxicity.^{15,24} While seafood, meat, grains, eggs,
112 and cereals are excellent sources of Se, Brazil nuts have the highest concentration.⁶
113 The Brazil nut tree (*Bertholletia excelsa*), a native species from South America, is
114 found mainly in the Brazilian Amazon region, which has a Se-rich soil that influences
115 the high Se content in the nuts and the Se status of the population.^{23,25} Nevertheless,
116 for this population, the higher intake that reflects plasma Se concentrations that could

117 reach 900 µg/L, with a median of 135 µg/L, is not toxic.²⁶ Some factors that could
118 explain the lack of selenosis in this population are as follows: (1) the population might
119 have adapted to a higher than average Se status through metabolic mechanisms; (2)
120 the high Se content might be protective against Hg exposure since plasma
121 selenoprotein P can bind Hg and reduce its bioavailability to target proteins²⁶; (3) this
122 population might have a specific gut microbiota profile due to their exposure to high
123 Se that helps excrete the excess Se more rapidly²⁷; (4) they might have
124 polymorphisms in genes that regulate Se metabolism and excretion.²⁷ The Brazil nut
125 tree is considered a secondary accumulator tree that can accumulate about 100 to
126 1,000 mg/Se/g⁻¹ of dry weight in their seeds. The organic forms of Se (C-Se-C
127 species) are predominantly present in this nut, which includes SeMet (the main Se
128 compound), SeMCys, and Se-lanthionine.²⁸ However, the Se content in nuts varies
129 according to the region of the Amazon rainforest where the Brazil nut tree was
130 planted.²⁹ Studies have shown the Se concentration of one Brazil nut from the
131 Brazilian Amazon rainforest can vary from 290 to 1,261 µg.^{19,30-33}

132 The dietary intake recommendation values proposed by the Food and Nutrition
133 Board of the Institute of Medicine (IOM) were based on the intake needed to
134 maximize plasma GPX3 activity.³⁴ The values of the estimated average requirement
135 (EAR), the recommended dietary allowance (RDA), tolerable upper intake level (UL),
136 no observed adverse effect level (NOAEL), and lowest observed adverse effect level
137 (LOAEL) for children, adults, pregnancy, and lactation are summarized in **Table 1**.

138

139 **BIOMARKERS OF SE NUTRITIONAL STATUS**

140 The evaluation of Se nutritional status remains a matter of debate since the
141 distribution of this mineral into selenoproteins depends on several factors, such as

142 the hierarchy system of incorporation, bioavailability from food sources, dietary
143 intake, health state, and the presence of genetic polymorphisms in selenoproteins.⁴
144 Overall, Se status involves Se dietary intake, Se content in tissues, Se function, and
145 excretion.²⁴ The current most commonly used biomarkers are 1) total Se
146 concentration in whole blood, plasma, serum, erythrocytes, or urine; 2) GPx activity
147 in plasma (GPx3), erythrocytes (GPx1), and whole blood (total GPx); and 3) plasma
148 selenoprotein P (SELENOP) levels.²⁴

149 A reliable marker of Se intake must to be sensitive to changes in Se status and
150 reflect the current intake through food. It should be noted that plasma Se levels can
151 be used to predict Se intake if SeMet is mostly consumed by using a linear
152 regression equation ($Se_{in, \mu g/kg0.75/day} = 0.44 + 0.03 \times Se_{plasma, ng/mL}$).²⁴ Food
153 questionnaires can also measure Se intake; nevertheless, the available food
154 composition tables do not address the huge geographical variation of Se content in
155 soil.

156 After absorption, Se can be found in tissues, such as whole blood, erythrocyte,
157 and plasma. In humans, whole blood Se is not the best biomarker option because it
158 does not reflect its biological function, executed through selenoproteins activity. The
159 evaluation of specific selenoproteins can thus provide a more precise diagnostic of
160 Se status.^{4,35} Erythrocyte Se represents a long-term evaluation of Se status since the
161 half-life of these cells is about 120 days.⁴

162 Several factors, such as geographical location, gender, age, race, BMI, smoking
163 status and alcohol consumption, affect plasma Se concentrations. Studies have
164 found a reduction in plasma Se concentration with age,³⁶ as well as in protein
165 malnutrition,³⁷ chronic inflammation,³⁸ in smokers,^{39,40} in obese individuals,^{39,41} in
166 African Americans,⁴² and in daily alcohol consumers.³⁶ Red wine consumers had

167 higher than average plasma Se levels in the SU.VI.MAX study conducted in
168 France.³⁹

169 The measurement of selenoproteins activity, involved mostly with redox control, is
170 the best option when evaluating Se status because this biomarker reflects Se
171 function. It is important to note that Se have biological effects that do not occur
172 through the selenoproteins.⁴³ In a xenograft model of prostate cancer, Se-
173 methylselenocysteine and methylseleninic acid inhibited tumor growth while selenite
174 and SeMet did not.⁴⁴ The direct biomarkers are GPx1 and GPx3 activities and
175 plasma SELENOP concentration.²⁴ GPx1 activity is a suitable biomarker in cases of
176 low Se status (plasma concentration < 60 µg/L) since the activity of this enzyme
177 cannot reach its maximal level in that range of Se concentration and can be
178 assessed in erythrocytes using spectrophotometry.⁴⁵ This biomarker is also effective
179 and sensitive for evaluating Se supplementation due to its rapid response observed
180 in a period of one to two weeks, depending on the baseline Se status and the
181 chemical form of Se administrated.^{24,35} The response of the biomarkers to different
182 chemical forms of Se has been reviewed extensively elsewhere and is not addressed
183 in this article.⁴⁶⁻⁵² GPx1 activity has been found to vary with gender and age, being
184 higher in females than males⁵³⁻⁵⁷ and females under 55 years than males and
185 females over 55 years.⁵⁸ GPx1 activity was reduced in smokers,^{56,58,59} in patients
186 with cardiovascular events⁵⁸ and in patients with asthma.⁶⁰

187 GPx3 is an extracellular isoform that the kidney produces by and is
188 responsible for around 10 - 25% of total plasma Se. The measurements of plasma
189 GPx3 activity and/or concentration can be both used as Se biomarkers and they
190 usually correlate with total plasma Se concentration.^{4,24} Regarding the two GPx
191 activities, it is essential to highlight that they reach a maximal activity at different

192 plasma Se concentrations: GPx1 around 80–120 µg Se/L⁶¹ and GPx3 around 70–90
193 µg Se/L.⁶² In this context, both activities are useful biomarkers of Se status to assess
194 a nutritional deficiency. GPx3 activity varies with age and gender, being lower in
195 adults between the ages of 40 and 49 years and obese females compared to adults
196 of other ages and obese males.⁴¹

197 SELENOP acts as the primary Se transporter to peripheral tissues, being the
198 only selenoprotein that can contain as many as 10 residues of Sec and comprises
199 40–60% of total plasma Se.⁴ While the measurement of plasma SELENOP
200 concentration is considered the most conclusive biomarker of Se status, no reference
201 values for it exist.^{24,63,64} SELENOP reaches a plateau when plasma Se concentration
202 is around 120 µg Se/L.^{52,65} Factors such as ethnicity and BMI affected SELENOP
203 concentrations, for example, SELENOP is reduced in African-Americans⁴² and obese
204 adults.⁶⁶

205 Urinary Se is a marker of Se excretion associated with plasma Se
206 concentration and Se intake. Results from balance studies confirm that urinary Se
207 represents 50–60% of the total amount excreted; Se intake can therefore be
208 estimated as twice the urinary Se.³⁵ Hair and toenails are tissues that accumulate Se,
209 being markers of Se retention, and are thus more useful as markers of longer
210 exposure over the past six to 12 months.^{6,62,67} Nevertheless, hair samples must be
211 analyzed carefully due to possible contamination from by chemical products, such as
212 Se-containing shampoos.^{6,24}

213

214 **THE CHOICE OF SE BIOMARKERS DEPENDS ON THE SE STATUS OF THE** 215 **POPULATION**

216 The choice of a specific biomarker to evaluate Se status must consider

217 several factors, such as the health status of the individual, the specific biological
218 function of selenoproteins, and the genetic polymorphisms.⁴ The use of different
219 biomarkers is an adequate approach because it provides information related to Se
220 nutritional status and the functionality of specific selenoproteins.²⁴ An ideal
221 measurement of Se status must reflect the amount available for the functional activity
222 of selenoproteins.³⁵ For instance, in populations with low plasma Se concentrations
223 (< 60 µg/L), more options of biomarkers are available because selenoproteins do not
224 reach their maximal activity. In this case, while plasma Se is an adequate option, so
225 is erythrocyte GPx1 activity, plasma GPx3 activity, and plasma SELENOP
226 concentration.⁶⁸

227 In individuals with adequate Se status and intake, the increase in Se
228 biomarkers does not depend on chemical forms of Se since almost all inorganic and
229 organic forms, including selenite in the presence of reduced glutathione (GSH), are
230 rapidly absorbed.⁴ SeMet appears to be more bioavailable because it is being
231 incorporated inespecifically into plasma proteins such as albumin. The raise in
232 plasma Se due to the increase in SeMet is directly correlated with the increase in Se
233 in albumin.²⁴ However, SeMet can raise plasma Se and SELENOP concentrations
234 even in those individuals with adequate Se status.^{24,48,52,69} The increase in those two
235 biomarkers is possible since its absorption occurs through a transcellular pathway
236 that transporters mediate and the elimination of inorganic species is increased,
237 while SeMet is retained and incorporated in an unspecific way into other proteins,
238 such as serum albumin and hemoglobin. SeMCys can also be absorbed through the
239 same process that SeMet contributes to the increased plasma Se.^{4,70} The
240 consumption of Se as SeMet in individuals with adequate Se status can therefore be
241 estimated using plasma Se concentrations as a biomarker.^{24,69} As to populations with

242 high Se exposure, the indicated biomarker is plasma Se concentration because all
243 selenoproteins reach their plateau with a plasma Se concentration of 150 µg/L. The
244 supplementation with 1,600 µg and 3,200 µg of Se yeast of individuals with baseline
245 plasma Se concentration of 135 and 129 µg/L, respectively, was able to increase this
246 biomarker.⁷¹

247

248 **FUNCTIONAL SINGLE NUCLEOTIDE POLYMORPHISMS AFFECTING** 249 **BIOMARKERS OF SE NUTRITIONAL STATUS**

250

251 ***Evidence of the functional consequences of some single nucleotide*** 252 ***polymorphisms in selenoproteins***

253 After the conclusion of the HGP, several genetic variations were discovered.
254 Within the five human DNA samples used for the entire HGP, more than 3 million
255 SNPs with an average density of 1/1,250 bp were discovered.⁸ Other initiatives to
256 map the entire diversity of the human genetic variation includes the International
257 Hapmap Project⁷² and the 1000 Genomes Project Consortium.⁷³ The latter observed
258 more than 85 million SNPs in a sample of 2,504 subjects with different ethnic
259 backgrounds.⁷³

260 Different types of polymorphisms occur the human genome, including SNPs,
261 short insertions/deletions (indels), and structural variants. By definition, a
262 polymorphic locus in a chromosome is one in which the most common variant occurs
263 in less than 99% of the population; in terms of the variant allele, the rarer allele must
264 occur in more than 1% of the population.^{74,75} The substitution of a single nucleotide in
265 the DNA sequence is the simplest and most common type of polymorphism, the
266 SNP. In the nutritional genomics field, the most studied type of genetic variation is

267 the SNP. Polymorphisms located in intron were thought not to affect the structure of
268 the final protein; however, this concept has changed because if the variation is
269 located in an intron close to the splicing junction, it will change the entire open
270 reading frame and, as a consequence, the entire sequence of aminoacids of the
271 protein after the SNP.⁷⁶ It is worth noting that most SNPs have no biological effect for
272 several reasons: they could be in exons and do not change the amino acid because
273 the genetic code is degenerated, or even if they change the amino acid, this
274 modification is not essential for the structure, stability, and function of the protein.^{76,77}
275 Concerning genes that encode selenoproteins, the great challenge is therefore to
276 discover SNPs that, alone or interacting with other SNPs, affect the expression or the
277 activity of these proteins that modulate Se nutritional status.⁷⁷ Single nucleotide
278 polymorphisms in at least 10 selenoprotein genes are believed to be associated with
279 the variation of several biomarkers of Se status.²⁴

280 One of the most studied SNPs in selenoprotein genes is the Pro198Leu in the
281 *GPX1* gene (rs1050450). It is a C > T substitution located in the coding region of the
282 gene that changes the amino acid proline to leucine in position 198 of the protein.⁷⁸
283 Previous studies have demonstrated that the presence of the rare allele T was
284 associated with a reduction in GPx1 activity^{59,79–84} and with a reduction in GPX1
285 mRNA expression.^{82,85,86} It is hypothesized that the change of the amino acid proline
286 to leucine alters the secondary and tertiary structures of the protein, affecting its
287 activity and stability.⁷⁹ Indeed, *in vitro* studies have confirmed a reduction in the
288 thermostability of the enzyme-containing the leu variant.⁸⁷

289 GPx4 is the only GPx isoform that can reduce phospholipid hydroperoxides in
290 the cell membrane.⁸⁸ A substitution C > T is located in the 3'UTR (rs713041), the
291 mRNA region important for Sec insertion. Experimental evidence, both *in vitro* and *in*

292 *vivo*, has demonstrated that this SNP has functional consequences. Levels of
293 lymphocyte lipoxygenase products were higher in individuals with the CC genotype
294 than in those with the TT genotype, and the C allele was associated with a higher risk
295 for colorectal cancer compared to the T allele.⁸⁹ In vitro studies have revealed that
296 *GPX4* transcripts that contain the C allele indicate a better ability to bind proteins
297 during translation, competing strongly with not only the transcripts that contain the T
298 allele but also the *GPX1* transcripts. Under a limitation of Se supply, this better ability
299 to bind proteins means that *GPX4* with the C allele have a preference for protein
300 synthesis.⁹⁰ In human endothelial cells, the T allele was associated with higher than
301 average levels of lipid hydroperoxides and was also more susceptible to oxidative
302 stress.⁹¹ In addition, the rare T allele was associated with a higher risk for breast
303 cancer⁹² and colorectal cancer compared to the C allele.⁹³

304 Two SNPs with functional consequences were described in the *SELENOP*
305 gene that encodes the plasma SELENOP, the main plasma Se transporter for tissues
306 and the brain. Both SNPs are G > A substitutions: one located in the coding region,
307 predicted to change the amino acid alanine to threonine at position 235 (rs3877899),
308 and the other located in the 3' UTR region, important for Sec insertion (rs7579).⁴¹ It is
309 hypothesized that rs3877899 regulates SELENOP stability and uptake through the
310 cells, and the rs7579 affects the synthesis of this selenoprotein.⁴¹ Plasma SELENOP
311 has two isoforms, the 50 kDa and the 60 kDa, with the second one containing the
312 Sec-rich domain.⁹⁴ The two SNPs in the *SELENOP* gene affect both isoforms. At
313 baseline, individuals with the GA genotype for rs3877899 had a lower proportion of
314 the SELENOP 60 kDa, with the Sec-rich domain. After Se supplementation with 200
315 µg of selenite for eight weeks, individuals with the AA genotype for rs7579 presented
316 a lower proportion of SELENOP 60 kDa compared to individuals with the GG

317 genotype.⁹⁵ In addition, rs7579 was associated with a higher than average risk of
318 developing prostate cancer.⁹⁶ Moreover, the presence of the rare allele A for rs7579
319 was associated with an increase in *SELENOP* mRNA expression^{82,86} and higher than
320 average cholesterol levels after supplementation with Brazil nuts⁹⁷, while the
321 presence of the rare allele A for rs3877899 was associated with an increase in
322 *SELENOP* mRNA expression⁸² and with lower levels of cholesterol after
323 supplementation with Brazil nuts.⁹⁷

324 The selenoprotein F (*SELENOF*), previously known as 15 kDa selenoprotein
325 (*SEP15*), has two functional polymorphisms located in the 3' UTR region (rs5845 and
326 rs5859) that are in linkage disequilibrium within the same haplotype, which means
327 that the presence of the rare allele for one SPN implicates the presence of the other
328 one. The first SNP is a G > A substitution at position 1,125 in the apical loop of the
329 SECIS element, and the second one is a C > T substitution at position 811.⁹⁸ The
330 variation in the apical loop (rs5845) might influence the efficiency of Sec
331 incorporation into proteins.⁹⁹ In vitro studies have verified that the TA haplotype was
332 less responsive to sodium selenite supplementation in NIH 3T3 mouse fibroblasts⁹⁹
333 and mesothelioma cells than the GC haplotype.¹⁰⁰ In addition, the polymorphism
334 rs5845 was associated with a higher risk of lung cancer in plasma Se concentrations
335 below 60 µg/L,¹⁰¹ an increased risk of colorectal cancer,¹⁰² lower scores for verbal
336 learning memory¹⁰³ and a higher histological tumor grade in patients who have
337 undergone radical prostatectomy compared to individuals with the normal
338 genotype.¹⁰⁴

339 Selenoprotein S (*SELENOS*), located in the endoplasmic reticulum (ER), is
340 associated with the protection of the ER from the stress that by misfolded proteins
341 cause¹⁰⁵ and with the control of the inflammatory response.^{106,107} A substitution C > T

342 occurs in the promoter region of the *SELENOS* gene (rs34713741) that has been
343 associated with an increased risk of rectal,¹⁰² colorectal,⁹³ and gastric cancer¹⁰⁸ as
344 well as ischemic stroke.¹⁰⁹ Another relevant polymorphism is the rs28665122, located
345 in the promoter region of the *SELENOS* gene, also known as -105G/A. This SNP has
346 been correlated with plasma IL-1, IL-6, and TNF- α levels¹⁰⁶, an increased
347 susceptibility to Hashimoto's Thyroiditis¹¹⁰, preeclampsia in Norwegian women¹⁰⁷
348 and an increased risk of gastric cancer.¹¹¹

349

350 ***Plasma Se***

351 Plasma Se is a short-term biomarker that reflects the current nutritional status
352 of this mineral.^{24,112} Since this biomarker is widely used to evaluate Se status and
353 responds to dietary intake, genetic variations that affect plasma Se should be
354 investigated as they can influence the assessment of Se nutritional status.

355 Lower plasma Se concentrations were associated with four SNPs in different
356 selenoproteins (rs1050450 [*GPX1*], rs3877899 and rs7579 [*SELENOP*] and
357 rs3471374 [*SELENOS*) and higher plasma Se with one SNP (rs7579 [*SELENOP*]). In
358 a study conducted with 261 adults from the United States with a mean age of 50
359 years, lower plasma Se concentrations were observed in subjects with the rare TT
360 genotype for the SNP in the antioxidant enzyme GPX1 Pro198Leu (rs1050450).⁶⁶ In
361 a Polish supplementation trial that included 95 adults with a mean age of 35 years
362 who were administered 200 μ g of SeMet a day for six months, the coding SNP in the
363 *SELENOP* gene (rs3877899) was associated with lower plasma Se only at baseline
364 in individuals with the rare genotype AA.¹¹³ In the SU.BRA.NUT trial, the association
365 of SNPs in selenoproteins with biomarkers of Se status was evaluated in 130 adults
366 after the supplementation with one unit of Brazil nut (~300–400 μ g/Se) for eight

367 weeks following a washout period of eight weeks. Two SNPs were associated with
368 lower plasma Se after only four weeks of Brazil nut intake: *SELENOP* gene (rs7579)
369 and *SELENOS* gene (rs34713741).³² In the SELGEN trial, the association of SNPs in
370 the *SELENOP* gene with biomarkers of Se status before and after supplementation
371 was investigated in 75 healthy adults from England with a mean age of 40 years, who
372 were supplemented with 200 µg of sodium selenite for six weeks following six weeks
373 of washout. Overall, individuals with the rare genotype AA for the 3' UTR on
374 *SELENOP* rs7579 had higher plasma Se concentrations after the intervention period
375 and two weeks of washout compared to individuals with the GG genotype.⁴¹

376

377 ***Erythrocyte Se***

378 Erythrocyte Se concentration is a biomarker of Se status that reflects long-
379 term Se intake.²⁴ Although it is a useful biomarker, it is not commonly used in studies
380 that investigate the association of SNPs with biomarkers of Se status in healthy
381 adults. Specifically for patients with systemic inflammatory response, erythrocyte Se
382 is a better biomarker than plasma Se since the acute phase response does not affect
383 it.¹¹⁴ Two studies have found this association. In the observational study, there was
384 an association between the coding SNP rs8179169, a substitution G > C that
385 changes the amino acid arginine to proline in position five of the protein (Arg5Pro) in
386 the *GPX1* gene, and erythrocyte Se concentrations: lower concentrations were
387 observed in individuals with the GC genotype.⁵⁴ In the SU.BRA.NUT trial, erythrocyte
388 Se concentration was associated with two SNPs: rs713041 (*GPX4*) and rs34713741
389 (*SELENOS*). The 3'UTR SNP in *GPX4* gene rs713041 was associated with lower
390 erythrocyte Se in T-carriers at baseline. Moreover, an increase in the variation ($\Delta 1_{[8}$
391 weeks nuts – baseline]) of erythrocyte Se concentration in T-carriers for rs34713741

392 occurred in the *SELENOS* gene, which means that in these individuals, erythrocyte
393 Se concentration was higher compared to the CC genotype after Se supplementation
394 with Brazil nuts; the T-carriers were more responsive to Se supplementation.³²

395

396 ***Erythrocyte GPx1 activity***

397 Erythrocyte GPx1 activity is a widely used biomarker of Se status and intake,
398 especially in cases of suspected deficiency.²⁴ While several studies have evaluated
399 the influence of SNPs in selenoprotein genes that can affect GPx1 activity, the most
400 studied is the rs1050450 in the *GPX1* gene (Pro198Leu).^{32,40,54,56,113,115,116} However,
401 SNPs in other selenoproteins have also been associated with alterations in GPx1
402 activity in healthy volunteers. These include rs713041 (*GPX4*),^{32,54,90} rs3877899,
403 rs7579 (*SELENOP*)^{32,40} and rs5845 (*SELENOF*)³². Overall, the presence of the rare
404 allele T or genotype TT for rs1050450 has been associated with lower GPx1 activity
405 in seven studies (see **Table 2**).^{32,40,56,83,113,115,116} In three of these studies, a gender-
406 SNP interaction was modulating GPx1 activity.^{54,56,83} Moreover, T-carriers for
407 rs1050450 in the *GPX1* gene had a reduction in GPx1 mRNA expression after
408 supplementation with Brazil nuts⁸⁶. A reduction in GPx1 activity was also associated
409 with rs5845 in the *SELENOF* gene in the SU.BRA.NUT trial during the washout
410 period³² and with rs3877899 in the *SELENOP* gene in adults from New Zealand.⁴⁰

411 The presence of the rare allele T for rs713041 (*GPX4*) was associated with
412 both higher^{32,40} and lower than average GPx1 activity.⁹⁰ It is initially surprising that
413 SNP in genes other than *GPX1* can affect GPx1 enzyme activity; nevertheless, the
414 hierarchy of selenoprotein expression could explain this result. Indeed,
415 selenoproteins compete with one another against components of the selenoprotein
416 synthesis machinery and for available Se, as the amino acid Sec, during the

417 translation process.^{88,117} The differences in the 3' UTR region, where the Sec
418 insertion occurs, are the main factor that drives this competition. Single nucleotide
419 polymorphisms in this specific region of Sec insertion can therefore change the
420 hierarchical order of selenoprotein expression.⁹¹ RNA-protein binding assays *in vitro*
421 demonstrated that the C-variant for rs713041 in *GPX4* transcripts bind to protein
422 more strongly than the T-variant and *GPX1* transcripts.⁹⁰ In addition, *GPX4* protein is
423 ranked high in the hierarchy of selenoprotein expression, which indicates that it has a
424 preference for protein synthesis when Se supply is scarce.¹¹⁷ Such evidence
425 suggests that in individuals with the C allele for rs713041 in the *GPX4* gene, the
426 synthesis of *GPX1* protein is expected to be lower because, during translation, the C
427 transcript for *GPX4* can compete more strongly against the *GPX1* transcript for Se
428 incorporation into *GPX4* protein, which means that Sec will be incorporated
429 preferentially into *GPX4* protein rather than *GPX1*. By contrast, in individuals with the
430 T allele for the *GPX4* SNP the opposite scenario occurs, changing the hierarchy: Sec
431 will be directed to *GPX1* synthesis because the T-transcript is not strong enough to
432 compete against *GPX1* during translation.^{90,91} In the SU.BRA.NUT trial, an increase
433 in the variation ($\Delta 1$ [8 weeks nuts – baseline]) of erythrocyte Se concentration in A-carriers for
434 rs7579 occurred in the *SELENOP* gene, which suggests that in these individuals,
435 erythrocyte Se concentration was higher compared to the GG genotype after Se
436 supplementation with Brazil nuts; A-carriers were more responsive to Se
437 supplementation.³²

438

439 ***Plasma GPx3 activity***

440 Studies conducted with healthy adults found an influence of genetic
441 polymorphisms in selenoprotein genes on GPx3 activity, and overall, the presence of

442 the rare allele for rs7579 (*SELENOP*), rs713041 (*GPX4*), and rs5845 (*SELENOF*)
443 was associated with a reduction in its activity. In the SELGEN trial, rs713041 (*GPX4*)
444 and rs7579 (*SELENOP*) were associated with lower GPx3 activity after the
445 supplementation and washout period.^{41,90} The same rationale for the influence of the
446 SNP in rs713041 (*GPX4*) on GPx1 activity could be applied to explain the influence
447 of SNPs in *SELENOP* and *SELENOF* on GPx3 activity. In the SU.BRA.NUT trial,
448 rs5845 (*SELENOF*) was associated with lower variation in GPx3 activity after the
449 intervention period ($\Delta 1_{[8 \text{ weeks nuts} - \text{baseline}]}$), which means that in T-carriers, the GPx3
450 activity was less responsive to Brazil nut supplementation compared to the CC
451 genotype.³² In a study conducted with healthy pregnant women in the United
452 Kingdom, A-carriers for rs3877899 (*SELENOP*) increased GPx3 activity after
453 supplementation with Se-yeast; in the placebo group, the A-carriers were able to
454 maintain their Se status measured by whole blood Se.¹¹⁸

455

456 ***Plasma Selenoprotein P***

457 Plasma SELENOP concentration is considered one of the best biomarkers of
458 short-term Se status and intake.⁶² Three SNPs have been associated with a
459 reduction in plasma SELENOP concentration: two on its gene (rs3877899 and
460 rs7579) and one in the *SELENOF* gene (rs5845). In the SELGEN trial, heterozygote
461 females for rs3877899 had lower plasma SELENOP concentrations than GA males.⁴¹
462 In healthy Americans, GA adults for rs7579 had lower plasma SELENOP than GG
463 and GA genotypes.⁶⁶ In the SU.BRA.NUT trial, T-carriers for rs5845 (*SELENOF*) had
464 a lower variation of plasma SELENOP concentration during the washout period ($\Delta 2_{[\text{washout} - \text{nuts}]}$),
465 which indicates that this biomarker dropped after Se withdrawal, being
466 more responsive to a reduction in Se availability.³² By contrast, the same two SNPs

467 on the *SELENOP* gene were associated with an increase in plasma SELENOP
468 concentrations after Se supplementation. An SNP-gender interaction occurred after
469 the supplementation: higher than average plasma SELENOP concentration was
470 associated with the GG genotype for rs3877899 in women^{41,116} and with the GA
471 genotype for rs7579 in men.⁴¹ In American adults, plasma SELENOP concentrations
472 were lower in GA individuals compared to GG individuals for rs3877899.⁶⁶ Moreover,
473 in A-carriers for rs7579, *SELENOP* mRNA expression was higher than in GG
474 individuals before and after Brazil nut intake.⁸⁶

475

476 **Conclusions**

477 This review provided an overview of the effects of functional SNPs in
478 selenoprotein genes on the most common biomarkers of Se nutritional status.
479 Evidence demonstrates a significant reduction of GPX1 activity in the presence of the
480 rare allele T for the coding SNP rs1050450 (*GPX1*). Concerning the other functional
481 SNPs, insufficient evidence prevents stating that some genotypes can modulate one
482 or more biomarkers of Se status.

483 As to the association between the reduction on GPX1 activity and the SNP
484 rs1050450 in the *GPX1* gene, non-RCT and RCT interventions and observational
485 studies with a baseline plasma Se below 100µg/L have confirmed this association;
486 however, in populations with high Se status, such as that of the United States, this
487 association has not been observed. One explanation is the saturation of
488 selenoproteins activity or concentration with plasma Se above 120 µg/L. Even with a
489 supplementation, populations with high Se status would not increase selenoprotein
490 activity because they are already at their maximal and the presence of the SNP
491 would not change this response.

492 Nutrigenetics studies have helped the great advances in Se biology of the past
493 two decades years. The ultimate goal of a more personalized nutritional
494 recommendation is closer to being realized than ever before. Nevertheless, more
495 research in this area must be encouraged and be integrated with other omics tools
496 (metabolomics, epigenomic, proteomic and transcriptomic) to better understand all
497 the data provided so far. When strong evidence on the effects of some genotypes on
498 biomarkers of Se status becomes available, it will likely be used to update the current
499 dietary recommendation based on not only the regional particularities but also on the
500 genetic characteristics of the population or even of individuals (personalized
501 nutrition).

502

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504

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508

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510

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518 *Table 1 Summary of Selenium dietary reference intake values*

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Life Stage Group	EAR (µg/day)	RDA (µg/day)	UL (µg/day)	NOAEL (µg/day)	LOAEL (µg/day)
Children and adolescents					
1 – 3 y	17	20	49	90	-
4 – 8 y	23	30	150	150	-
9 – 13 y	35	40	280	280	-
>14 y	45	55	400	800	900
Adults					
19 – 70 y	45	55	400	800	900
> 70 y	45	55	400	800	900
Pregnancy					
14 – 50 y	49	60	400	800	900
Lactation					
14 – 50 y	59	70	400	800	900

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521 EAR = estimated average requirement; RDA = recommended dietary allowance, UL =
 522 tolerable upper intake level; NOAEL = no observed adverse effect level; LOAEL = lowest
 523 observed adverse effect level.³⁴

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Table 2 Observational studies evaluating the effects of functional SNPs on biomarkers of Se status in healthy subjects.

Country	Population	Plasma Se (µg/L)	SNP	Genotype % and MAF (allele)	Main results	Reference
Sweden	214 adults, age and BMI n.i	n.i	<i>GPX1</i> rs1050450 (C > T)	53/ 40/ 7 MAF (T): 0.27	↔ GPx1 activity with genotypes	Forsberg et al. (2000) ¹¹⁹
USA	115 Asians, 63 Caucasians, 20 Hispanics, 19 Others, adults, 17-21 y, BMI n.i, M= 102, F= 129	n.i	<i>GPX1</i> rs1050450 (C > T)	A: 86/ 11/ 3 C: 46/ 46/ 8 H: 60/ 35/ 5 O: 58/ 21/ 21	No effect of ethnicity on GPx1 activity ↓ GPx activity in males with TT genotype All: 13.16 U/g Hb. Males/females: 2.49/ 2.62 ^a , 2.60/ 2.65 ^a , 2.20/ 2.63 * ^a (CC, CT, TT)	Bastaki et al. (2006) ⁸³
Brazil (North Region)	149 women, mean age 26 y, BMI= 22.9	49.7	<i>GPX1</i> rs1050450 (C > T)	58/ 35/ 7 MAF (T): 0.25	↔ Se biomarkers with genotypes	Rocha et al. (2016) ¹²⁰
Brazil (Southeast Region)	116 adults, mean age 28 y, BMI= 23.1, M= 44, F= 72	53.2	<i>GPX1</i> rs1050450 (C > T)	48/ 48/ 4 MAF (T): 0.28	↑ GPx1 activity in females with CC genotype	Donadio et al. (2016) ⁵⁴
			<i>GPX1</i> rs8179169 (G > C)	29/ 70/ 0 MAF (C): 0.35	↓ erythrocyte Se in GC genotype ↑ GPx1 activity in females with GC genotype	
			<i>GPX4</i> rs713041 (C > T)	39/ 45/ 16 MAF (T): 0.15	↑ GPx1 activity in females with CC genotype	
Brazil (Northeast Region)	343 adults, mean age 24y, BMI= 22.8, M= 145, F= 198,	54.0	<i>GPX1</i> rs1050450 (C > T)	52/ 39/ 9 MAF (T): 0.28	↓ GPx1 activity in T-carriers ↑ ORAC levels in T-carriers	Almondes et al. (2018) ¹¹⁵
Poland	405 adults, mean age 57 y, BMI n.i, M= 282, F=	54.4	<i>GPX1</i> rs1050450	48/ 42/ 10 MAF (T):	↓ correlation of GPx1 activity and Plasma Se in TT genotype	Jablonksa et al.

	123		(C > T)	0.31		(2009) ¹²¹
Scotland	66 adults, 20-60 y, gender and BMI not informed	67.6	<i>GPX4</i> rs713041 (C > T)	34/ 41/ 25 MAF (T): 0.45	↔ GPx4 activity with genotypes	Villette et al. (2002) ⁸⁹
Denmark	295 adults, mean age 34 y, BMI n.i, M=134, F= 161	83	<i>GPX1</i> rs1050450 (C > T)	33/ 33/ 34 MAF (T): 0.31	↓ GPx1 activity in females T-carriers	Malling et al. (2009) ⁵⁶
New Zealand	503 males, mean age 52 y, BMI= 26.7	111.6	<i>GPX1</i> rs1050450 (C > T)	48/ 44/ 8 MAF (T): 0.30	↓ correlation between GPx1 activity and serum Se in TT genotype	Karunasingh e et al. (2012) ⁴⁰
					↑ correlation between GPx1 activity and serum Se in CT genotype	
					↑ correlation between DNA damage and serum Se in CC genotype	
					↑ correlation between Serum Se and GPx1 activity in CT genotype	
			<i>GPX4</i> rs713041 (C > T)	31/ 48/ 21 MAF (T): 0.45	↓ trend in DNA damage with increasing serum Se in TT genotype	
			<i>SELENOP</i> rs3877899 (G > A)	57/ 38/ 5 MAF (A): 0.25	↓ correlation between GPx1 activity and serum Se in GG genotype ↑ correlation between serum Se and TR activity in GG genotype	
			<i>SELENOP</i> rs5845 (G > A) 1125G>A	63/ 34/ 3 MAF (A): 0.20	↑ correlation between serum Se and GPx1 activity in CC genotype	
USA	195 adults, mean age 64 y, 82% males,	136.6	<i>GPX4</i> rs713041 (C > T)	27/ 48/ 24 MAF (T): 0.49	↔ Se biomarkers with genotypes (GPx1 activity, GPx3 activity, SELENOP, serum Se)	Takata et al. (2012) ¹²²
					<i>SELENOP</i> rs3877899 (G > A)	

USA	261 adults, mean age 50 y, BMI= 27.4, M= 106, F= 155	142	<i>GPX1</i>	46/ 43/ 11	↓ plasma Se in TT genotype	Combs et al. (2012) ⁶⁶
			rs1050450	MAF (T):	All: 142.0 ng/mL. 145.9/ 139.5/ 135.7* (CC/CT/TT)	
			(C > T)	0.33		
			<i>GPX4</i>	28/ 52/ 20	↔ Se biomarkers with genotypes (plasma Se, GPx3, SELENOP, buccal Se and urinary Se)	
			rs713041	MAF (T):		
			(C > T)	0.46		
<i>SELENOP</i>	58/ 45/ 16	↔ Se biomarkers with genotypes (plasma Se, GPx3, SELENOP, buccal Se and urinary Se)				
rs3877899	MAF (A):					
(G > A)	0.23					
<i>SELENOP</i>	44/ 44/ 12	↓ Plasma SELENOP in GA genotype				
rs7579	MAF (A):	All: 3.43 ng/mL				
(G > A)	0.34	3.62/ 3.24* / 3.49 (GG/ GA / AA)				
<i>SELENOP</i>	65/ 31/ 4	↓ buccal Se in CT genotype				
rs5845	MAF (A):	All: 8.39 ng/mg prot				
(G > A)	0.19	8.77/ 7.65* / 8.27 (GG/ GA / AA)				
	1125G>A					

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532 ↔ no association, ↑ increased, ↓ decreased. *: statistically different at p< 0.05. #: number of genotyped samples were smaller than the total
533 N^a: mean log activity.

534 BMI: body mass index (kg/m²), F: females, GPx: Glutathione Peroxidase enzyme, GPX: Glutathione Peroxidase gene, M: males, MAF: minor
535 allele frequency, nd: not determined, n.i: not informed, ORAC: oxygen radical absorbance capacity, measurement of antioxidant capacity in
536 biological samples, Se: selenium, SELENOP: Plasma Selenoprotein P, SELENOP: Selenoprotein F (former Selenoprotein 15kDa), SELENOP:
537 Selenoprotein P, SELENOS: Selenoprotein S, suppl: supplementation, wks: weeks. Studies are ordered according to plasma Se concentration

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542 **Table 3 Intervention trials (Non-RCT and RCT) evaluating the effects of functional SNPs on biomarkers of Se status in healthy adults.**

Study design/ Country	Intervention	Population	Plasma Se (µg/L) before/after	SNPs	Genotypes % and MAF (allele)	Main results	References
Non-RCT Intervention trial/ Poland	Supplementation with 200 µg Se yeast a day for six wks + six wks of washout	95 adults, mean age 35 y, BMI= 23.8, M= 43, F= 52	62.6/ 93.8	<i>GPX1</i> rs1050450 (C>T) Pro198Leu	41/ 37/ 22 MAF (T): 0.41	↓ GPx1 activity in TT genotype ↔ plasma Se and SELENOP with genotypes	Jablonska et al. (2015) ¹¹³
				<i>SELENOP</i> rs3877899 (G>A) Ala235Thr	48/ 31/ 21 MAF (A): 0.36	↓ plasma Se in AA genotype at baseline All: 62.6 µg/L. 66.3/ 68.9/ 52.0* (GG/GA/AA)	
RCT/ Denmark	Supplementation with 1,000 g of raw fish and mussel (50 µg Se/day) for 26 wks	94 adults, mean age 61 y, BMI= 26.3, M= 28, F= 21 (from intervention group only)	84.7/ n.i	<i>GPX1</i> rs1050450 (C>T) Pro198Leu	47/ 45/ 8 MAF (T): 0.30	↓ GPx1 activity in T-carriers at baseline for intervention group ↔ whole blood Se and SELENOP with genotypes	Kopp et al. (2018) ¹¹⁶
				<i>GPX4</i> rs713041 (C>T)	33/ 51/ 16 MAF (T): 0.30	↔ Se biomarkers with genotypes at baseline and after supplementation	
				<i>SELENOP</i> rs3877899 (G>A) Ala235Thr	61/ 37/ 2 MAF (A): 0.19	↑ higher SELENOP and whole blood Se in GG compared to A-carriers at week 26 in the intervention group	
				<i>SELENOP</i> rs7579 (G>A)	49/ 45/ 6 MAF (A): 0.29	↔ Se biomarkers with genotypes at baseline and after supplementation	
Non-RCT Intervention	Supplementation with 100 µg sodium	40 adults, mean age 40y, BMI 68%	90.8/ 107.4	<i>GPX4</i> rs713041	55/nd/ 45 MAF (T): nd	↓ GPx4 activity during washout in TT genotype	Méplan et al (2007,

trial/ England	selenite for six wks and six wks of washout	<25, M= 16, F= 24		(C>T)		↓ GPx1 activity in females TT after 2 wks of washout ↓ GPx3 activity in TT genotype	2008) ^{41,90}
				<i>SELENOP</i> rs3877899 (G>A) Ala235Thr	53/ 53/ 7 MAF (A): 0.20	↓ GPx4 activity in females GA vs males GG ↓ lower SELENOP in females GA vs males GA ↑ higher SELENOP in females GG vs males GG	
				<i>SELENOP</i> rs7579 (G>A)	49/ 43/ 8 MAF (A): 0.29	↑ plasma Se in AA genotype (post suppl. and 2 wks of washout) ↑ SELENOP in males GA vs females GA after supplementation ↑ SELENOP in GA genotype with BMI <25 ↓ GPx3 activity in males AA (pre, post and 2 wks of washout)	
Non-RCT Intervention trial/ Brazil	Supplementation with one Brazil nut (400µg Se) a day for eight wks + eight wks of washout	130 adults, mean age 29y, BMI = 23.3, M= 32, F= 98	96.7/ 267	<i>GPX1</i> rs1050450 (C>T) Pro198Leu	54/ 40/ 6 MAF (T): 0.26	↓ GPx1 activity in T-carriers	Donadio et al. (2018) ³²
				<i>GPX4</i> rs713041 (C>T)	38/ 42/ 20 MAF (T): 0.40	↓ Erythrocyte Se in T-carriers at baseline ↑ GPx1 activity in T-carriers during washout period ↑ variation in GPx1 activity in females T-carriers after washout; values did not drop after Se withdrawal in females T-carriers	
				<i>SELENOP</i> rs3877899	54/ 36/ 10 MAF (A):	↓ plasma Se in A-carriers	

				(G>A) Ala235Thr	0.28		
				<i>SELENOP</i> rs7579 (G>A)	38/ 42/ 19 MAF (A): 0.40	↓ plasma Se in A-carriers after 4 wks of supplementation ↑ variation in GPx1 activity in A-carriers after supplementation: GPx1 activity was more responsive to Se supplementation in A-carriers	
				<i>SELENOP</i> rs5845 (G>A) 1125G>A	42/ 46/ 12 MAF (A): 0.35	↓ GPx1 activity in T-carriers during washout period ↓ variation in GPx3 activity in T-carriers after supplementation: GPx3 activity was less responsive to Se supplementation in T-carriers ↓ variation in SELENOP in T-carriers after washout: SELENOP was more responsive to changes in Se availability in T-carriers	
				<i>SELENOS</i> rs34713741 (C>T)	54/ 38/ 8 MAF (T): 0.27	↓ Plasma Se in T-carriers after four wks of supplementation ↑ variation in Erythrocyte Se in T-carriers after supplementation: Erythrocyte Se was more responsive to Se supplementation in T-carriers	
RCT/ USA	Supplementation with 0, 50, 100 or 200 µg of L-SeMet a day for 1y	243 adults, mean age 50 y, BMI = 27.4, M= 98, F= 145	142/ 291.6	<i>GPX1</i> rs1050450 (C>T) Pro198Leu	46/ 43/ 11 MAF (T): 0.33	↓ plasma Se in TT genotype at baseline All: 142.0 µg/L. 145.9/ 139.5/ 135.7* (CC/CT/TT) ↑ Urinary Se in TT genotype after 3months of supplementation	Combs et al. (2012) ⁶⁹
				<i>GPX4</i>	28/ 52/ 20	↔ Se biomarkers with genotypes at	

rs713041 (C>T)	MAF (T): 0.46	baseline and after supplementation
<i>SELENOP</i> rs3877899 (G>A)	58/ 38/ 4 MAF (A): 0.23	↔ Se biomarkers with genotypes at baseline and after supplementation
Ala235Thr		
<i>SELENOP</i> rs7579 (G>A)	44/ 44/ 12 MAF (A): 0.34	↔ Se biomarkers with genotypes at baseline and after supplementation
<i>SELENOP</i> rs5845 (G>A)	65/ 31/ 4 MAF (A): 0.19	↔ Se biomarkers with genotypes at baseline and after supplementation
1125G>A		

543

544 ↔ no association, ↑ increased, ↓ decreased. *: statistically different at p< 0.05.

545 BMI: body mass index (kg/m²), F: females, GPx: Glutathione Peroxidase enzyme, GPX: Glutathione Peroxidase gene, M: males, MAF: minor
546 allele frequency, nd: not determined, n.i: not informed, Se: selenium, *SELENOP*: Plasma Selenoprotein P, *SELENOP*: Selenoprotein P, *SELENOP*: Selenoprotein P, *SELENOS*: Selenoprotein S, suppl: supplementation, wks: weeks. Studies are ordered
547 according to baseline plasma Se concentration.

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550 **REFERENCES**

- 551 1. Forstrom JW, Zakowski JJ, Tappel AL. Identification of the Catalytic Site
552 of Rat Liver Glutathione Peroxidase as Selenocysteine. *Biochemistry*.
553 1978;17(13):2639-2644. doi:10.1021/bi00606a028
- 554 2. Rayman MP, Blundell-Pound G, Pastor-Barriuso R, et al. A Randomized
555 Trial of Selenium Supplementation and Risk of Type-2 Diabetes, as
556 Assessed by Plasma Adiponectin. *PLoS One*. 2012;7(9).
557 doi:10.1371/journal.pone.0045269
- 558 3. Fairweather-Tait SJ, Bao Y, Broadley MR. Selenium in Human Health and
559 Disease. *Antioxid Redox Signal*. 2011;14(7):3-26. doi:10.1007/978-3-319-
560 95390-8_1
- 561 4. Roman M, Jitaru P, Barbante C. Selenium biochemistry and its role for
562 human health. *Metallomics*. 2014;6(1):25-54. doi:10.1039/c3mt00185g
- 563 5. Stoffaneller R, Morse NL. A review of dietary selenium intake and
564 selenium status in Europe and the Middle East. *Nutrients*.
565 2015;7(3):1494-1537. doi:10.3390/nu7031494
- 566 6. Navarro-Alarcon M, Cabrera-Vique C. Selenium in food and the human
567 body: A review. *Sci Total Environ*. 2008;400(1-3):115-141.
568 doi:10.1016/j.scitotenv.2008.06.024
- 569 7. Méplan C. Selenium and chronic diseases: A nutritional genomics
570 perspective. *Nutrients*. 2015;7(5):3621-3651. doi:10.3390/nu7053621
- 571 8. Venter JC, Adams MD, Myers EW, et al. The sequence of the human
572 genome. *Science*. 2001;291(5507):1304-1351.
573 doi:10.1126/science.1058040
- 574 9. Papp LV, Lu J, Holmgren A, Khanna KK. From selenium to
575 selenoproteins: synthesis, identity, and their role in human health.
576 *Antioxid Redox Signal*. 2007;9(7):775-806. doi:10.1089/ars.2007.1528
- 577 10. Brigelius-Flohé R, Flohé L. Selenium and redox signaling. *Arch Biochem*
578 *Biophys*. 2017;617:48-59. doi:10.1016/j.abb.2016.08.003
- 579 11. Kryukov GV, Castellano S, Novoselov SV, et al. Characterization of
580 mammalian selenoproteomes. *Science*. 2003;300(5624):1439-1443.
581 doi:10.1126/science.1083516
- 582 12. Fernandes J, Hu X, Ryan Smith M, et al. Selenium at the redox interface
583 of the genome, metabolome and exposome. *Free Radic Biol Med*.
584 2018;127:215-227. doi:10.1016/j.freeradbiomed.2018.06.002
- 585 13. Kretz-Remy C, Arrigo AP. Selenium: a key element that controls NF-
586 kappa B activation and I kappa B alpha half life. *BioFactors*. 2001;14(1-
587 4):117-125.
- 588 14. Duntas LH. Selenium and inflammation: underlying anti-inflammatory
589 mechanisms. *Horm Metab Res*. 2009;41(6):443-447. doi:10.1055/s-0029-
590 1220724

- 591 15. Rayman MP. Selenium and human health. *Lancet*. 2012;379(9822):1256-
592 1268. doi:10.1016/S0140-6736(11)61452-9
- 593 16. Brown KM, Arthur JR. Selenium, selenoproteins and human health: a
594 review. *Public Health Nutr*. 2001;4(2B):593-599.
- 595 17. Beckett GJ, Arthur JR. Selenium and endocrine systems. *J Endocrinol*.
596 2005;184(3):455-465. doi:10.1677/joe.1.05971
- 597 18. Steinbrenner H, Sies H. Selenium homeostasis and antioxidant
598 selenoproteins in brain: Implications for disorders in the central nervous
599 system. *Arch Biochem Biophys*. 2013;536(2):152-157.
600 doi:10.1016/j.abb.2013.02.021
- 601 19. Cardoso BR, Apolinário D, Bandeira V da S, et al. Effects of Brazil nut
602 consumption on selenium status and cognitive performance in older
603 adults with mild cognitive impairment: a randomized controlled pilot trial.
604 *Eur J Nutr*. 2015;55(1):107-116. doi:10.1007/s00394-014-0829-2
- 605 20. Foresta C, Flohé L, Garolla A, et al. Male fertility is linked to the
606 selenoprotein phospholipid hydroperoxide glutathione peroxidase. *Biol*
607 *Reprod*. 2002;67(3):967-971. doi:10.1095/biolreprod.102.003822
- 608 21. Brigelius-Flohé R, Maiorino M. Glutathione peroxidases. *Biochim Biophys*
609 *Acta*. 2013;1830(5):3289-3303. doi:10.1016/j.bbagen.2012.11.020
- 610 22. Rayman MP. Food-chain selenium and human health: emphasis on
611 intake. *Br J Nutr*. 2008;100(2):254-268. doi:10.1017/S0007114508939830
- 612 23. Lemire M, Fillion M, Barbosa F, et al. Elevated levels of selenium in the
613 typical diet of Amazonian riverside populations. *Sci Total Environ*.
614 2010;408(19):4076-4084. doi:10.1016/j.scitotenv.2010.05.022
- 615 24. Combs GF. Biomarkers of Selenium Status. *Nutrients*. 2015;7:2209-2236.
616 doi:10.3390/nu7042209
- 617 25. Cardoso BR, Duarte GBS, Reis BZ, et al. Brazil nuts: Nutritional
618 composition, health benefits and safety aspects. *Food Res Int*.
619 2017;100(August):9-18. doi:10.1016/j.foodres.2017.08.036
- 620 26. Lemire M, Philibert A, Fillion M, et al. No evidence of selenosis from a
621 selenium-rich diet in the Brazilian Amazon. *Environ Int*. 2012;40(1):128-
622 136. doi:10.1016/j.envint.2011.07.005
- 623 27. Rayman MP. Selenium intake, status, and health: a complex relationship.
624 *Hormones*. 2020;19(1):9-14. doi:10.1007/s42000-019-00125-5
- 625 28. Lima LW, Stonehouse GC, Walters C, et al. Selenium accumulation,
626 speciation and localization in Brazil nuts (*Bertholletia excelsa* H.B.K.).
627 *Plants*. 2019;8:289. doi:10.3390/plants8080289
- 628 29. Silva Junior EC, Wadt LHO, Silva KE, et al. Natural variation of selenium
629 in Brazil nuts and soils from the Amazon region. *Chemosphere*.
630 2017;188(November):650-658. doi:10.1016/j.chemosphere.2017.08.158
- 631 30. Cominetti C, de Bortoli MC, Garrido AB, et al. Brazilian nut consumption
632 improves selenium status and glutathione peroxidase activity and reduces

- 633 atherogenic risk in obese women. *Nutr Res.* 2012;32(6):403-407.
634 doi:10.1016/j.nutres.2012.05.005
- 635 31. Stockler-Pinto MB, Mafra D, Moraes C, et al. Brazil nut (*Bertholletia*
636 *excelsa*, H.B.K.) improves oxidative stress and inflammation biomarkers
637 in hemodialysis patients. *Biol Trace Elem Res.* 2014;158(1).
638 doi:10.1007/s12011-014-9904-z
- 639 32. Donadio JLS, Rogero MM, Guerra-Shinohara EM, et al. Genetic variants
640 in selenoprotein genes modulate biomarkers of selenium status in
641 response to Brazil nut supplementation (the SU.BRA.NUT study). *Clin*
642 *Nutr.* 2018;38(2):539-548. doi:10.1016/j.clnu.2018.03.011
- 643 33. Duarte GBS, Reis BZ, Rogero MM, et al. Consumption of Brazil nuts with
644 high selenium levels increased inflammation biomarkers in obese women:
645 a randomized controlled trial. *Nutrition.* February 2019.
646 doi:10.1016/J.NUT.2019.02.009
- 647 34. Institute of Medicine. Food and Nutrition Board. *Dietary Reference Intakes*
648 *for Vitamin C, Vitamin E, Selenium, and Carotenoids.*; 2000.
649 doi:10.17226/9810
- 650 35. Thomson CD. Assessment of requirements for selenium and adequacy of
651 selenium status: a review. *Eur J Clin Nutr.* 2004;58(3):391-402.
652 doi:10.1038/sj.ejcn.1601800
- 653 36. Lloyd B, Lloyd RS, Clayton BE. Effect of smoking, alcohol, and other
654 factors on the selenium status of a healthy population. *J Epidemiol*
655 *Community Health.* 1983;37(3):213-217. doi:10.1136/jech.37.3.213
- 656 37. Mathias P, Jackson A. Selenium deficiency in kwashiorkor. *Lancet.*
657 1982;1:1312-1313. doi:10.1016/s0140-6736(84)90925-5
- 658 38. Maehira F, Luyo GA, Miyagi I, et al. Alterations of serum selenium
659 concentrations in the acute phase of pathological conditions. *Clin Chim*
660 *Acta.* 2002;316(1-2):137-146. doi:10.1016/S0009-8981(01)00744-6
- 661 39. Arnaud J, Bertrais S, Roussel AM, et al. Serum selenium determinants in
662 French adults: the SU.VI.M.AX study. *Br J Nutr.* 2006;95(2):313-320.
663 doi:10.1079/BJN20051528
- 664 40. Karunasinghe N, Han DY, Zhu S, et al. Serum selenium and single-
665 nucleotide polymorphisms in genes for selenoproteins: Relationship to
666 markers of oxidative stress in men from Auckland, New Zealand. *Genes*
667 *Nutr.* 2012;7(2):179-190. doi:10.1007/s12263-011-0259-1
- 668 41. Méplan C, Crosley LK, Nicol F, et al. Genetic polymorphisms in the
669 human selenoprotein P gene determine the response of selenoprotein
670 markers to selenium supplementation in a gender-specific manner (the
671 SELGEN study). *FASEB J.* 2007;21(12):3063-3074. doi:10.1096/fj.07-
672 8166com
- 673 42. Hargreaves MK, Liu J, Buchowski MS, et al. Plasma selenium biomarkers
674 in low income black and white americans from the southeastern United
675 States. *PLoS One.* 2014;9(1):1-9. doi:10.1371/journal.pone.0084972

- 676 43. Christensen MJ. Selenium and prostate cancer prevention: What next - If
677 anything? *Cancer Prev Res.* 2014;7(8):781-785. doi:10.1158/1940-
678 6207.CAPR-14-0197
- 679 44. Li GX, Lee HJ, Wang Z, et al. Superior in vivo inhibitory efficacy of
680 methylseleninic acid against human prostate cancer over
681 selenomethionine or selenite. *Carcinogenesis.* 2008;29(5):1005-1012.
682 doi:10.1093/carcin/bgn007
- 683 45. Paglia DE, Valentine WN. Studies on the quantitative and qualitative
684 characterization of erythrocyte glutathione peroxidase. *J Lab Clin Med.*
685 1967;70(1):158-169.
- 686 46. Meltzer HM, Norheim G, Bibow K, et al. The form of selenium determines
687 the response to supplementation in a selenium replete population. *Eur J*
688 *Clin Nutr.* 1990;44(6):435-446.
- 689 47. Persson-Moschos M, Alfthan G, Akesson B. Plasma selenoprotein P
690 levels of healthy males in different selenium status after oral
691 supplementation with different forms of selenium. *Eur J Clin Nutr.*
692 1998;52(5):363-367. doi:10.1038/sj.ejcn.1600565
- 693 48. Burk RF, Norsworthy BK, Hill KE, et al. Effects of chemical form of
694 selenium on plasma biomarkers in a high-dose human supplementation
695 trial. *Cancer Epidemiol Biomarkers Prev.* 2006;15(4):804-810.
696 doi:10.1158/1055-9965.EPI-05-0950
- 697 49. Xia Y, Hill KE, Byrne DW, et al. Effectiveness of selenium supplements in
698 a low selenium area of China. *Am J Clin Nutr.* 2005;81(4):829-834.
- 699 50. Ravn-Haren G, Bügel S, Krath BN, et al. A short-term intervention trial
700 with selenate, selenium-enriched yeast and selenium-enriched milk:
701 effects on oxidative defence regulation. *Br J Nutr.* 2008;99(4):883-892.
702 doi:10.1017/S0007114507825153
- 703 51. Rayman MP, Infante HG, Sargent M. Food-chain selenium and human
704 health: spotlight on speciation. *Br J Nutr.* 2008;100(2):238-253.
705 doi:10.1017/S0007114508922522
- 706 52. Hurst R, Armah CN, Dainty JR, et al. Establishing optimal selenium
707 status: results of a randomized, double-blind, placebo-controlled trial.
708 *Am J Clin Nutr.* 2010;91(4):923-931. doi:10.3945/ajcn.2009.28169
- 709 53. Rush JWE, Sandiford SD. Plasma glutathione peroxidase in healthy
710 young adults: influence of gender and physical activity. *Clin Biochem.*
711 2003;36(5):345-351. doi:10.1016/S0009-9120(03)00039-0
- 712 54. Donadio JLS, Guerra-Shinohara EM, Rogero MM, et al. Influence of
713 gender and SNPs in GPX1 gene on biomarkers of selenium status in
714 healthy Brazilians. *Nutrients.* 2016;8(5):81. doi:10.3390/nu8050081
- 715 55. Massafra C, Gioia D, De Felice C, et al. Gender related differences in
716 erythrocyte glutathione peroxidase activity in healthy subjects. *Clin*
717 *Endocrinol (Oxf).* 2002;57(5):663-667.
- 718 56. Malling TH, Sigsgaard T, Andersen HR, et al. Sex determines the

- 719 influence of smoking and gene polymorphism on glutathione peroxidase
720 activity in erythrocytes. *Scand J Clin Lab Invest.* 2009;69(2):295-302.
721 doi:10.1080/00365510802632155
- 722 57. Habif S, Mutaf I, Turgan N, et al. Age and gender dependent alterations in
723 the activities of glutathione related enzymes in healthy subjects. *Clin*
724 *Biochem.* 2001;34(8):667-671. doi:10.1016/S0009-9120(01)00279-X
- 725 58. Blankenberg S, Rupprecht HJ, Bickel C, et al. Glutathione peroxidase 1
726 activity and cardiovascular events in patients with coronary artery
727 disease. *N Engl J Med.* 2003;349(17):1605-1613.
728 doi:10.1056/NEJMoa030535
- 729 59. Ravn-Haren G, Olsen A, Tjønneland A, et al. Associations between GPX1
730 Pro198Leu polymorphism, erythrocyte GPX activity, alcohol consumption
731 and breast cancer risk in a prospective cohort study. *Carcinogenesis.*
732 2006;27(4):820-825. doi:10.1093/carcin/bgi267
- 733 60. Nadeem A, Chhabra SK, Masood A, et al. Increased oxidative stress and
734 altered levels of antioxidants in asthma. *J Allergy Clin Immunol.*
735 2003;111(1):72-78. doi:10.1067/mai.2003.117
- 736 61. Ashton K, Hooper L, Harvey LJ, et al. Methods of assessment of selenium
737 status in humans: A systematic review. *Am J Clin Nutr.*
738 2009;89(Suppl):2025S-39S. doi:10.3945/ajcn.2009.27230F
- 739 62. Hurst R, Collings R, Harvey LJ, et al. EURRECA-Estimating selenium
740 requirements for deriving dietary reference values. *Crit Rev Food Sci*
741 *Nutr.* 2013;53(April 2014):1077-1096.
742 doi:10.1080/10408398.2012.742861
- 743 63. Burk RF, Hill KE. Selenoprotein P-Expression, functions, and roles in
744 mammals. *Biochim Biophys Acta.* 2009;1790(11):1441-1447.
745 doi:10.1016/j.bbagen.2009.03.026
- 746 64. Xia Y, Hill KE, Li P, et al. Optimization of selenoprotein P and other
747 plasma selenium biomarkers for the assessment of the selenium
748 nutritional requirement: A placebo-controlled, double-blind study of
749 selenomethionine supplementation in selenium-deficient Chinese
750 subjects. *Am J Clin Nutr.* 2010;92(3):525-531.
751 doi:10.3945/ajcn.2010.29642
- 752 65. Kipp AP, Strohm D, Brigelius-Flohé R, et al. Revised reference values for
753 selenium intake. *J Trace Elem Med Biol.* 2015;32:195-199.
754 doi:10.1016/j.jtemb.2015.07.005
- 755 66. Combs GF, Watts JC, Jackson MI, et al. Determinants of selenium status
756 in healthy adults. *Nutr J.* 2011;10:75. doi:10.1186/1475-2891-10-75
- 757 67. Filippini T, Ferrari A, Michalke B, et al. Toenail selenium as an indicator of
758 environmental exposure: A cross-sectional study. *Mol Med Rep.*
759 2017;15(5):3405-3412. doi:10.3892/mmr.2017.6388
- 760 68. Elsom R, Sanderson P, Hesketh JE, et al. Functional markers of selenium
761 status: UK Food Standards Agency workshop report. *Br J Nutr.*

- 762 2006;96(5):980-984. doi:10.1017/BJN20061893
- 763 69. Combs GF, Jackson MI, Watts JC, et al. Differential responses to
764 selenomethionine supplementation by sex and genotype in healthy
765 adults. *Br J Nutr.* 2012;107(10):1514-1525.
766 doi:10.1017/S0007114511004715
- 767 70. Müller SM, Dawczynski C, Wiest J, et al. Functional Biomarkers for the
768 Selenium Status in a Human Nutritional Intervention Study. *Nutrients.*
769 2020;12:676. doi:10.3390/nu12030676
- 770 71. Reid ME, Stratton MS, Lillico AJ, et al. A report of high-dose selenium
771 supplementation: Response and toxicities. *J Trace Elem Med Biol.*
772 2004;18(1):69-74. doi:10.1016/j.jtemb.2004.03.004
- 773 72. International Hapmap Consortium. The International HapMap Project.
774 *Nature.* 2003;426(6968):789-796. doi:10.1038/nature02168
- 775 73. Auton A, Abecasis GR, Altshuler DM, et al. A global reference for human
776 genetic variation. *Nature.* 2015;526(7571):68-74.
777 doi:10.1038/nature15393
- 778 74. Schork NJ, Fallin D, Lanchbury JS. Single nucleotide polymorphisms and
779 the future of genetic epidemiology. *Clin Genet.* 2000;58(4):250-264.
780 doi:10.1034/j.1399-0004.2000.580402.x
- 781 75. Kauwell GPA. Emerging concepts in nutrigenomics: a preview of what is
782 to come. *Nutr Clin Pract.* 2005;20(1):75-87.
783 doi:10.1177/011542650502000175
- 784 76. Corella D, Ordovas JM. Basic Concepts in Molecular Biology Related to
785 Genetics and Epigenetics. *Rev Esp Cardiol.* 2017;70(9):744-753.
786 doi:10.1016/j.recesp.2017.02.034
- 787 77. Hesketh J. Nutrigenomics and selenium: gene expression patterns,
788 physiological targets, and genetics. *Annu Rev Nutr.* 2008;28:157-177.
789 doi:10.1146/annurev.nutr.28.061807.155446
- 790 78. Moscow JA, Schmidt L, Ingram DT, et al. Loss of heterozygosity of the
791 human cytosolic glutathione peroxidase I gene in lung cancer.
792 *Carcinogenesis.* 1994;15(12):2769-2773. doi:10.1016/0169-
793 5002(95)98726-Q
- 794 79. Ratnasinghe D, Tangrea JA, Andersen MR, et al. Glutathione peroxidase
795 codon 198 polymorphism variant increases lung cancer risk. *Cancer Res.*
796 2000;60(22):6381-6383.
- 797 80. Jablonska E, Gromadzinska J, Peplonska B, et al. Lipid peroxidation and
798 glutathione peroxidase activity relationship in breast cancer depends on
799 functional polymorphism of GPX1. *BMC Cancer.* 2015;15(1):1-12.
800 doi:10.1186/s12885-015-1680-4
- 801 81. Hansen RD, Krath BN, Frederiksen K, et al. GPX1 Pro198Leu
802 polymorphism, erythrocyte GPX activity, interaction with alcohol
803 consumption and smoking, and risk of colorectal cancer. *Mutat Res.*
804 2009;664(1-2):13-19. doi:10.1016/j.mrfmmm.2009.01.009

- 805 82. Cardoso BR, Busse AL, Hare DJ, et al. Pro198Leu polymorphism affects
806 the selenium status and GPx activity in response to Brazil nut intake.
807 *Food Funct.* 2016;7(2):825-833. doi:10.1039/c5fo01270h
- 808 83. Bastaki M, Huen K, Manzanillo P, et al. Genotype-activity relationship for
809 Mn-superoxide dismutase, glutathione peroxidase 1 and catalase in
810 humans. *Pharmacogenet Genomics.* 2006;16(4):279-286.
811 doi:10.1097/01.fpc.0000199498.08725.9c
- 812 84. Cominetti C, de Bortoli MC, Purgatto E, et al. Associations between
813 glutathione peroxidase-1 Pro198Leu polymorphism, selenium status, and
814 DNA damage levels in obese women after consumption of Brazil nuts.
815 *Nutrition.* 2011;27(9):891-896. doi:10.1016/j.nut.2010.09.003
- 816 85. Hamanishi T, Furuta H, Kato H, et al. Functional variants in the
817 glutathione peroxidase-1 (GPx-1) gene are associated with increased
818 intima-media thickness of carotid arteries and risk of macrovascular
819 diseases in Japanese type 2 diabetic patients. *Diabetes.*
820 2004;53(9):2455-2460. doi:10.2337/diabetes.53.9.2455
- 821 86. Donadio JLS, Rogero MM, Cockell S, et al. Influence of genetic variations
822 in selenoprotein genes on the pattern of gene expression after
823 supplementation with Brazil nuts. *Nutrients.* 2017;9(7):739.
824 doi:10.3390/nu9070739
- 825 87. Zhuo P, Goldberg M, Herman L, et al. Molecular consequences of genetic
826 variations in the glutathione peroxidase 1 selenoenzyme. *Cancer Res.*
827 2009;69(20):8183-8190. doi:10.1158/0008-5472.CAN-09-1791
- 828 88. Bellinger FP, Raman AV, Reeves MA, et al. Regulation and function of
829 selenoproteins in human disease. *Biochem J.* 2009;422(1):11-22.
830 doi:10.1042/BJ20090219
- 831 89. Villette S, Kyle JAM, Brown KM, et al. A novel single nucleotide
832 polymorphism in the 3' untranslated region of human glutathione
833 peroxidase 4 influences lipoxygenase metabolism. *Blood Cells Mol Dis.*
834 2002;29(2):174-178. doi:10.1006/bcmd.2002.0556
- 835 90. Méplan C, Crosley LK, Nicol F, et al. Functional effects of a common
836 single-nucleotide polymorphism (GPX4c718t) in the glutathione
837 peroxidase 4 gene: interaction with sex. *Am J Clin Nutr.* 2008;87(4):1019-
838 1027.
- 839 91. Crosley LK, Bashir S, Nicol F, et al. The single-nucleotide polymorphism
840 (GPX4c718t) in the glutathione peroxidase 4 gene influences endothelial
841 cell function: Interaction with selenium and fatty acids. *Mol Nutr Food*
842 *Res.* 2013;57(12):2185-2194. doi:10.1002/mnfr.201300216
- 843 92. Udler M, Maia AT, Cebrian A, et al. Common germline genetic variation in
844 antioxidant defense genes and survival after diagnosis of breast cancer. *J*
845 *Clin Oncol.* 2007;25(21):3015-3023. doi:10.1200/JCO.2006.10.0099
- 846 93. Méplan C, Hughes DJ, Pardini B, et al. Genetic variants in selenoprotein
847 genes increase risk of colorectal cancer. *Carcinogenesis.*
848 2010;31(6):1074-1079. doi:10.1093/carcin/bgq076

- 849 94. Mostert V, Lombeck I, Abel J. A novel method for the purification of
850 selenoprotein P from human plasma. *Arch Biochem Biophys.*
851 1998;357(2):326-330. doi:10.1006/abbi.1998.0809
- 852 95. Méplan C, Nicol F, Burtle BT, et al. Relative abundance of selenoprotein
853 P isoforms in human plasma depends on genotype, se intake, and cancer
854 status. *Antioxid Redox Signal.* 2009;11(11):2631-2640.
855 doi:10.1089/ars.2009.2533
- 856 96. Steinbrecher A, Méplan C, Hesketh J, et al. Effects of selenium status
857 and polymorphisms in selenoprotein genes on prostate cancer risk in a
858 prospective study of European men. *Cancer Epidemiol Biomarkers Prev.*
859 2010;19(11):2958-2968. doi:10.1158/1055-9965.EPI-10-0364
- 860 97. Donadio JLS, Rogero MM, Guerra-Shinohara EM, et al. SEPP1
861 polymorphisms modulate serum glucose and lipid response to Brazil nut
862 supplementation. *Eur J Nutr.* 2018;57(5):1873-1882. doi:10.1007/s00394-
863 017-1470-7
- 864 98. Gladyshev VN, Jeang K, Wootton JC, et al. A New Human Selenium-
865 containing Protein. Purification, characterization and cDNA sequence. *J*
866 *Biol Chem.* 1998;273(15):8910-8915.
- 867 99. Hu YJ, Korotkov K V, Mehta R, et al. Distribution and functional
868 consequences of nucleotide polymorphisms in the 3'-untranslated region
869 of the human Sep15 gene. *Cancer Res.* 2001;61(5):2307-2310.
- 870 100. Apostolou S, Klein JO, Mitsuuchi Y, et al. Growth inhibition and induction
871 of apoptosis in mesothelioma cells by selenium and dependence on
872 selenoprotein SEP15 genotype. *Oncogene.* 2004;23(29):5032-5040.
873 doi:10.1038/sj.onc.1207683
- 874 101. Jablonska E, Gromadzinska J, Sobala W, et al. Lung cancer risk
875 associated with selenium status is modified in smoking individuals by
876 Sep15 polymorphism. *Eur J Nutr.* 2008;47(1):47-54. doi:10.1007/s00394-
877 008-0696-9
- 878 102. Sutherland A, Kim DH, Relton C, et al. Polymorphisms in the
879 selenoprotein S and 15-kDa selenoprotein genes are associated with
880 altered susceptibility to colorectal cancer. *Genes Nutr.* 2010;5(3):215-223.
881 doi:10.1007/s12263-010-0176-8
- 882 103. Rocha TJ da, Blehm CJ, Bamberg DP, et al. The effects of interactions
883 between selenium and zinc serum concentration and SEP15 and
884 SLC30A3 gene polymorphisms on memory scores in a population of
885 mature and elderly adults. *Genes Nutr.* 2014;9(1):377.
886 doi:10.1007/s12263-013-0377-z
- 887 104. Ekoue DN, Ansong E, Liu L, et al. Correlations of SELENOF and
888 SELENOP genotypes with serum selenium levels and prostate cancer.
889 *Prostate.* 2018;78(4):279-288. doi:10.1002/pros.23471
- 890 105. Bos SD, Kloppenburg M, Suchiman E, et al. The role of plasma cytokine
891 levels, CRP and Selenoprotein S gene variation in OA. *Osteoarthr Cartil.*
892 2009;17(5):621-626. doi:10.1016/j.joca.2008.10.007

- 893 106. Curran JE, Jowett JBM, Elliott KS, et al. Genetic variation in selenoprotein
894 S influences inflammatory response. *Nat Genet.* 2005;37(11):1234-1241.
895 doi:10.1038/ng1655
- 896 107. Moses EK, Johnson MP, Tømmerdal L, et al. Genetic association of
897 preeclampsia to the inflammatory response gene SEPS1. *Am J Obstet*
898 *Gynecol.* 2008;198(3):1-5. doi:10.1016/j.ajog.2007.09.024
- 899 108. Mao H, Cui R, Wang X. Association analysis of selenoprotein S
900 polymorphisms in Chinese Han with susceptibility to gastric cancer. *Int J*
901 *Clin Exp Med.* 2015;8(7):10993-10999.
- 902 109. Li XX, Guan HJ, Liu JP, et al. Association of selenoprotein S gene
903 polymorphism with ischemic stroke in a Chinese case-control study.
904 *Blood Coagul Fibrinolysis.* 2015;26(2):131-135.
905 doi:10.1097/MBC.0000000000000202
- 906 110. Santos LR, Durães C, Mendes A, et al. A polymorphism in the promoter
907 region of the selenoprotein S gene (SEPS1) contributes to hashimoto's
908 thyroiditis susceptibility. *J Clin Endocrinol Metab.* 2014;99(4):719-723.
909 doi:10.1210/jc.2013-3539
- 910 111. Shibata T, Arisawa T, Tahara T, et al. Selenoprotein S (SEPS1) gene -
911 105G>A promoter polymorphism influences the susceptibility to gastric
912 cancer in the Japanese population. *BMC Gastroenterol.* 2009;9:2.
913 doi:10.1186/1471-230X-9-2
- 914 112. Robberecht H, Cauwenbergh R Van, Hermans N. Blood selenium levels
915 and factors influencing concentration values. *Trace Elem Electrolytes.*
916 2012;29(3). doi:10.5414/TE0X1237
- 917 113. Jablonska E, Raimondi S, Gromadzinska J, et al. DNA damage and
918 oxidative stress response to selenium yeast in the non-smoking
919 individuals: a short-term supplementation trial with respect to GPX1 and
920 SEPP1 polymorphism. *Eur J Nutr.* 2015:1-16. doi:10.1007/s00394-015-
921 1118-4
- 922 114. Stefanowicz FA, Talwar D, O'Reilly DSJ, et al. Erythrocyte selenium
923 concentration as a marker of selenium status. *Clin Nutr.* 2013;32(5):837-
924 842. doi:10.1016/j.clnu.2013.01.005
- 925 115. Almondes KGS, Cardoso BR, Cominetti C, et al. The redox balance of
926 healthy Brazilian adults is associated with GPX1 Pro198Leu and -602A/G
927 polymorphisms, selenium status, and anthropometric and lifestyle
928 parameters. *Food Funct.* 2018;9(10):5313-5322. doi:10.1039/c8fo01621f
- 929 116. Kopp TI, Outzen M, Olsen A, et al. Genetic polymorphism in
930 selenoprotein P modifies the response to selenium-rich foods on blood
931 levels of selenium and selenoprotein P in a randomized dietary
932 intervention study in Danes. *Genes Nutr.* 2018;13(1):1-10.
933 doi:10.1186/s12263-018-0608-4
- 934 117. Schomburg L, Schweizer U. Hierarchical regulation of selenoprotein
935 expression and sex-specific effects of selenium. *Biochim Biophys Acta.*
936 2009;1790(11):1453-1462. doi:10.1016/j.bbagen.2009.03.015

- 937 118. Mao J, Vanderlelie JJ, Perkins AV, et al. Genetic polymorphisms that
938 affect selenium status and response to selenium supplementation in
939 United Kingdom pregnant women. *Am J Clin Nutr.* 2016;103(1):100-106.
940 doi:10.3945/ajcn.115.114231
- 941 119. Forsberg L, de Faire U, Marklund SL, et al. Phenotype determination of a
942 common Pro-Leu polymorphism in human glutathione peroxidase 1.
943 *Blood Cells Mol Dis.* 2000;26(5):423-426. doi:10.1006/bcmd.2000.0325
- 944 120. Rocha A V., Rita Cardoso B, Zavarize B, et al. GPX1 Pro198Leu
945 polymorphism and GSTM1 deletion do not affect selenium and mercury
946 status in mildly exposed Amazonian women in an urban population. *Sci*
947 *Total Environ.* 2016;571:801-808. doi:10.1016/j.scitotenv.2016.07.054
- 948 121. Jablonska E, Gromadzinska J, Reszka E, et al. Association between
949 GPx1 Pro198Leu polymorphism, GPx1 activity and plasma selenium
950 concentration in humans. *Eur J Nutr.* 2009;48(6):383-386.
951 doi:10.1007/s00394-009-0023-0
- 952 122. Takata Y, King IB, Lampe JW, et al. Genetic Variation in GPX1 Is
953 Associated with GPX1 Activity in a Comprehensive Analysis of Genetic
954 Variations in Selenoenzyme Genes and Their Activity and Oxidative
955 Stress in Humans. *J Nutr.* 2012;142(3):419-426.
956 doi:10.3945/jn.111.151845
- 957