



Review article

Genetic polymorphisms in amyotrophic lateral sclerosis: Evidence for implication in detoxification pathways of environmental toxicants



Efthimios Dardiotis^{a,*,1}, Vasileios Siokas^{a,1}, Maria Sokratous^a, Zisis Tsouris^a, Amalia Michalopoulou^a, Athina Andravizou^a, Metaxia Dastamani^a, Styliani Ralli^a, Marco Vinceti^{b,c}, Aristidis Tsatsakis^d, Georgios M. Hadjigeorgiou^a

^a Department of Neurology, Laboratory of Neurogenetics, University of Thessaly, University Hospital of Larissa, Larissa, Greece

^b Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

^c Department of Epidemiology, Boston University School of Public Health, Boston, USA

^d Laboratory of Toxicology, School of Medicine, University of Crete, 71003 Heraklion, Greece

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease of the central nervous system, characterized by progressive loss of motor neurons, and occurring in both sporadic and familial form. The origin of the disease is unknown, though increasing evidence suggests that the interaction between genetic and environmental factors may increase susceptibility to ALS, including its sporadic form. Although genetic mutations have been correlated to the familial type of ALS, relatively little is known about the sporadic type (sALS). Genetic factors concerning pesticide metabolism and heavy metal detoxification are increasing the susceptibility to sALS. This review focuses on the genes implicated in metabolic detoxification pathways of environmental toxicants and their potential role in ALS susceptibility.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a heterogeneous group of neurodegenerative disorders (Hardiman et al., 2017; Sabatelli et al., 2016). It is considered to be the third most common neurodegenerative disease and the most frequent form of motor neuron disease with onset in the adulthood (Renton et al., 2014). ALS is characterized by progressive loss of motor neurons and rapidly progressive paralysis (Appel et al., 2011). It remains a very serious health problem, as within 2 to 3 years after the first symptoms, respiratory failure leads to death (Rowland and Shneider, 2001). Despite the fact that the cause of ALS still remains unknown, accumulative evidence suggests that genetic and environmental factors may be involved and interact to increase the susceptibility to ALS development (Peters et al., 2015; Zarei et al., 2015).

At genetic level, ALS can be classified into familial ALS (fALS), which constitutes approximately 10% of all ALS cases and sporadic ALS (sALS), with no evident genetic linkage, which accounts for 90% of all ALS cases (Chen et al., 2013). Genetic mutations were found to be responsible for fALS under autosomal dominant, autosomal recessive or X-linked mode of inheritance (Chen et al., 2013; Renton et al., 2014;

Taylor et al., 2016). Recently, a considerable effort has been made in order to elucidate the genetic susceptibility of sALS. Candidate gene association studies (CGASs) and genome-wide association studies (GWASs) have led to the identification of several genetic loci that may modify the risk of sALS (Chen et al., 2013; Mitropoulos et al., 2017; Nicolas et al., 2018; Renton et al., 2014).

Quite a few exogenous factors such as smoking, antioxidants, physical exercise & fitness, body mass index, electromagnetic fields, head trauma, metabolic and inflammatory diseases, viral infections, metals and pesticide exposure have been incriminated for possible contribution to ALS development (Ingre et al., 2015; Su et al., 2016; Vinceti et al., 2012). There is evidence that polymorphisms may modify the effect of environmental exposures to the risk of disease development (Kelada et al., 2003). The interplay between genetic and environmental factors and epigenetic modifications may have an impact on ALS susceptibility (Al-Chalabi and Hardiman, 2013; Paez-Colasante et al., 2015; Zarei et al., 2015; Zufiria et al., 2016). A few studies, with a variety in design (case-control, cohort, perspective, meta-analysis and systematic reviews) have demonstrated an association between ALS and pesticides, heavy metals, mercury and xenobiotics (Bozzoni et al., 2016; Capozzella et al., 2014; Deziel et al., 2015; Gibb and O'Leary, 2014;

* Corresponding author at: Department of Neurology, University Hospital of Larissa, Faculty of Medicine, University of Thessaly, Biopolis, Mezourlo Hill, Larissa 41100, Greece.
E-mail address: edar@med.uth.gr (E. Dardiotis).

¹ Equal contribution.

Krewski et al., 2017; Yu et al., 2014). However, there are also studies that have failed to reveal any association (Capozzella et al., 2014; Vinceti et al., 2017a; Vinceti et al., 2017b; Yu et al., 2014). The review by Bozzoni et al. concluded that there is strong evidence that pesticides have a crucial role in ALS development and that they are significant risk factors for neurodegeneration (Bozzoni et al., 2016). In contrast, the meta-analysis by Capozzella et al. has failed to prove a strong correlation between exposure to pesticides and ALS risk, as only a mild association was revealed (Capozzella et al., 2014). Moreover, Kamel et al. have indicated that ALS risk may depend on the kind of the pesticide (Kamel et al., 2012). There is also accumulative body of epidemiologic evidence that long-term pesticide exposure (even in low doses) predisposes to several neurodegenerative diseases (Baltazar et al., 2014; Zaganas et al., 2013). Long term exposure to organochlorine and to organophosphate pesticides may have a crucial role in Motor neuron Disease development (Kanavouras et al., 2011). Regarding the role of heavy metals (selenium, mercury, cadmium and iron) in ALS, despite the large number of studies, only a few of them have revealed an association (Bozzoni et al., 2016; Trojsi et al., 2013; Vinceti et al., 2014). Additionally, both xenobiotic metabolism pathways and genetic variation, which affects xenobiotic metabolism, may confer susceptibility to ALS (Kasperavičiute et al., 2007).

It is possible that the divergence in findings regarding the effects of pesticide exposure, heavy metals and xenobiotic metabolism on ALS risk may result from the genetic variability among the studied populations. Pesticide to gene interaction has been demonstrated by genetic association studies as well as by animal models (Dardiotis et al., 2013b). The aim of the present review is to discuss the current knowledge by focusing on genes that predispose to ALS development and are probably implicated in toxicity mechanisms and detoxification metabolic pathways of environmental toxicants.

2. Methods-study identification and selection

We searched PubMed for peer-reviewed articles, published in English language through December 2017, concerning human studies on ALS and polymorphisms across genes that are implicated to detoxification pathways of environmental toxicants. Our search included “amyotrophic lateral sclerosis” and “polymorphisms”, in combination with the following terms: “pesticides”, “lead”, “heavy metals”, “iron”, “toxicity” and “oxidative stress”, as free words. Last literature search was performed on December 31st, 2017. Additionally, reference lists of all retrieved articles were examined in order to identify studies missing from our initial database search. Published studies (case-control candidate gene association studies, gene-environment studies, meta-analyses, genome wide association studies, mutational screenings, cases only studies) between 1996 and 2016 were included. Baseline characteristics from studies regarding PON1, PON2 and PON3 genes are summarized in Table 1. Baseline characteristics from studies regarding ALAD, VDR, SNCA, MT family genes, MTF-1, GSS, FMO, SOD1, HFE, PGC-1 α , Nrf2, Transferrin, GSTs, ACHE, BCHE, NTE, FAH, CNR1, AADACL1, AFMID, APEH, CYP1A, CYP1B1, CYP2B6, CYP2C, CYP2D6, CYP2E1 and CYP3A are presented in Table 2.

3. Results & discussion

3.1. PON1, PON2 and PON3

Paraoxonase-1 gene: Paraoxonase-1 (PON1) is a serum calcium dependent esterase enzyme that is synthesized primarily in the liver and carried by high density lipoproteins (HDLs) (Costa et al., 2013). Its main function is to catalyze hydrolysis of the active metabolites (oxons) of some organophosphates including parathion, diazinon and chlorpyrifos (Costa et al., 2013). Hydrolysis of these products leads to the metabolites: diethylphosphate (DEP), trichloropyridinol (TCP), methylpyrimidinol (MHP) and para-nitrophenol (PNP) (Androutsopoulos

et al., 2011). Variants across PON1 gene have been reported to influence the concentration of paraoxonase-1 enzyme in serum, the protein stability and/or its catalytic activity (Dardiotis et al., 2013b). Rs662 (Q192R) and rs854560 (L55M) are non-synonymous functional coding polymorphisms that affect PON1 expression, catalytic function and plasma levels (Adkins et al., 1993; Androutsopoulos et al., 2011; Dardiotis et al., 2013b). The isoform with arginine (R) at 192 breaks down paraoxon, while the isoform with glutamine (Q) at 192 is more efficient in breaking down sarin, diazoxon and soman (Adkins et al., 1993; Androutsopoulos et al., 2011; Dardiotis et al., 2013b; Morahan et al., 2007b). The other functional polymorphism rs854560 (L55M) influences PON1 plasma levels (Adkins et al., 1993; Androutsopoulos et al., 2011; Dardiotis et al., 2013b; Morahan et al., 2007b). More precisely, individuals with methionine (M) at the position 55 reveal decreased expression, lower levels and reduced activity of PON1 (Adkins et al., 1993; Androutsopoulos et al., 2011; Dardiotis et al., 2013b; Morahan et al., 2007b). The 3D model of the PON1 normal and mutant proteins [resulting from rs662 (Q192R) and rs854560 (L55M)] based on SWISS-MODEL protein structure software (<http://www.swissmodel.expasy.org/>) and the main pathophysiology of the hydrolysis of chlorpyrifos-oxon, paraoxon and diazoxon by PON1 to DEP and other secondary metabolites are depicted in Fig. 1.

Rs662 (Q192R) and rs854560 (L55M) SNPs have also been associated with other neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis (MS) (Menini and Gugliucci, 2014). A recent meta-analysis also provides strong evidence that the PON1 rs705379 is associated with the risk of AD (Nie et al., 2017). However, the results of case-control studies and meta-analyses remain conflicting (Lee et al., 2015; Liu et al., 2012; Menini and Gugliucci, 2014; Pi et al., 2012; Wills et al., 2009; Zintzaras and Hadjigeorgiou, 2004). L55M and Q192R variants have been found to increase the risk of organophosphate toxicity in a population-dependent manner (You et al., 2013). Moreover, decreased PON1 activity has been associated with I102V PON1 polymorphism as well as with the risk alleles of the promoter polymorphisms rs705379 (−108T > C) and rs705381 (−162G > A) across the 5' regulatory-region (Brophy et al., 2001; Cronin et al., 2007; Marchesani et al., 2003; Morahan et al., 2007b). These findings suggest a possible functional effect of the aforementioned SNPs across PON1.

Two case-control studies examined the possibility of increased ALS susceptibility among individuals with specific PON1 polymorphisms rendering them more vulnerable to the organophosphate-induced neurotoxic effects (Diekstra et al., 2009; Morahan et al., 2007b). Morahan et al. examined 143 sALS cases and 143 controls. Pesticide/herbicide exposure was estimated according to participants' self-reports. For the susceptibility allele, the following interactive effects were observed, regarding the risk of sALS as clinical endpoint: a) for the promoter polymorphisms 832 g > a, −162 g > a and −108c > t, when the exposed to pesticides group was compared to the non-exposed group, b) for Q192R, when the high-dose and non-exposed groups were compared and c) for the promoter polymorphisms (909 g > c, −832 g > a, −162 g > a and −108c > t), when the low-dose and non-exposed groups were compared. However, no gene-environmental interactions were revealed by the genotype or haplotype levels or when the high-dose group was compared to the non-exposed one (with the exception of Q192R). Hence, the authors suggested that this effect is small and further analysis of other SNPs is of great necessity (Morahan et al., 2007b). In the case-control models of this study, T allele of −108c > t was overrepresented in sALS patients compared to controls. Moreover, a trend towards association with promoter haplotypes was observed. More precisely, haplotypes that decrease PON1 expression were associated with sALS, whereas haplotypes that increase PON1 expression were reported in controls (Morahan et al., 2007b). Diekstra et al. hypothesized that ALS patients living near agricultural fields would be more exposed to pesticides than those who live in urban areas. Therefore, they recruited 98 ALS patients in total (49 from urban

Table 1
Baseline characteristics of studies investigating the association between ALS risk and PON1, PON2 and PON3 genes.

Author (year)	Gene	Polymorphisms	Type of study	Ethnicity/participants	Main results
Morahan (2006)	PON1	promoter (g-909c, g-832a, rs705381, rs705379), coding (rs854560, rs662, 1102V)	Case-control and gene-environment study	Caucasian (Australian)/143 sALS and 143 controls	Promoter haplotypes and allele -108t, decreasing PON1 were associated with sALS Haplotypes increasing PON1 expression were associated with controls
Saeed (2006)	PON1, PON2, PON3, DYNC111	PON1 (rs2237582, rs662, rs854560, rs854565, rs705382) PON2 (rs6954345, rs2299263, rs11981433, rs2299267) PON3 (rs4141217, rs3757708, rs978903, rs10487132, rs2072200) DYNC111 (rs1869050, rs1685818, rs2283010) rs662	Case-control and family-based cohort	North Americans/203 unaffected parents-affected child triads (trios), 247 discordant sibpairs, 284 sALS and 504 spousal-community controls	Allelic gene-environment interactions between promoter SNPs and pesticide/herbicide exposure No association reported in case-control models analysis Rs10487132 (PON3) and rs11981433 (PON2) were associated with sALS in the trio model (parents-affected child triad) Rs10487132 (PON3) was associated with sALS in 450 nuclear pedigrees comprising trios and discordant sibpairs
Slowik (2006)	PON1	DYNC111 (rs1869050, rs1685818, rs2283010) rs662	Case-control	Caucasian (Polish)/166 sALS and 437 controls	R alleles were overrepresented in sALS Genotype with R allele was significantly associated with sALS at additive and recessive modes of inheritance [(OR = 1.36, 95%CI = 1.03–1.78, p = 0.034) and (OR = 1.86, 95%CI = 1.02–3.38, p = 0.04), respectively]
Slowik (2006)	PON1, PON2	PON1 (rs662, rs854560), PON2 (rs6954345)	Case-control	Caucasian (Polish)/185 sALS and 437 controls	R allele of PON1 Q192R polymorphism was associated with sALS in recessive, additive, and dominant models. C allele of PON2 C311S polymorphism was associated with sALS in dominant and additive models
Gronin (2006)	PON1, PON2, PON3	PON1 (rs662, rs854560, rs705379, rs705381), PON2 (rs6954345, rs12026), PON3 (rs10487132)	Case-control	Irish Caucasian/221 sALS and 202 controls	R-C haplotype was overrepresented among sALS patients Rs854560 PON1 and rs10487132 PON3 were associated with sALS [(OR = 1.52, 95%CI = 1.13–2.04, p = 0.006) and (OR = 1.36, 95%CI = 1.02–1.82, p = 0.03) respectively] The haplotype of rs854560 and rs10487132 and the haplotype of rs854560, rs705381 and rs10487132, was found to be associated with sALS [(OR = 1.7, 95%CI = 1.19–2.43, p = 0.005) and (OR = 1.63, 95%CI = 1.09–2.45, p = 0.02), respectively]
Landers (2008)	PON1	rs854543, rs854549, rs2237582, rs662, rs854560, rs2074351, rs854565, rs2299261, rs705381, rs705382, rs4141217, rs916864, rs3757708, rs10487132, rs2072200, rs987539, rs2286233, rs11981433, rs43037, rs10953147	Case-control	Caucasian (US, UK)/835 sALS and 924 controls	Rs2074351 and rs705382 (uncorrected p = 0.0016 and 0.0022, respectively) were associated with sALS 5-SNP haplotype: (rs854565/rs2299261/rs705381/rs705382/rs4141217) haplotype (p = 2.42E-04) was significantly associated with sALS
Valdmanis (2008)	PON1, PON2, PON3	PON1 (rs854548, rs854555, rs2269829, rs662, rs854560, rs854570, rs705381, rs705382) PON2 (rs11977702, rs6954345/rs7493, rs2068604, rs2237585, rs11981433, rs3757707) PON3 (rs757158, rs4141217, rs10953143, rs978903, rs10487132, rs11764079)	Case-control	France/480 cases and 475 controls Quebec/159 cases and 95 controls Sweden/558 cases and 506 controls	A constructed from SNPs at the C-terminal portion across PON2 (PON2 C311S including) haplotype was significantly associated with ALS in the French (p = 0.0075) and Quebec (p = 0.026) populations and in combined of three populations cohort (p = 1.69 × 10 ⁻⁶).
Willis (2009)	PON1, PON2, PON3	PON1 (rs854548, rs662, rs854560, rs705381, rs757158), PON2 (rs11981433), PON3 (rs978903)	Meta-analysis	4,037 ALS cases and 4,609 controls (including genome-wide association data from 2,018 ALS cases and 2,425 controls)	Negative

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Table 1 (continued)

Author (year)	Gene	Polymorphisms	Type of study	Ethnicity/participants	Main results
Diekstra (2009)	PON1	rs662, rs854560, rs6954345, and rs11981433	Case-only analysis and gene-environment interaction study	English/98 ALS	Strong association with population density observed for rs854560 (L55M) and weaker for rs662 (Q192R)
Zawiślak (2010)	PON1, PON2	rs705381	Case-control	Polish/259 ALS and 694 controls	Negative
Ricci (2011)	PON1, PON2, PON3	PON1 (rs854560, rs662), PON2 (rs6954345)	Case-control	Italians/350 sALS and 376 controls	Negative
Chen (2012)	PON1, PON2, PON3	PON1 (rs662, rs705381, rs705382, rs854548, rs854560), PON2 (rs7493, rs11981433), PON3 (rs757158, rs10487132)	Case-control	Chinese/373 sALS and 248 controls	Negative
van Blitterswijk (2012)	PON1, PON3	PON1 (rs854560, rs72552788, rs13306698, rs3917541, rs3917594, rs662), PON3 (rs17886586, rs13226149, rs11970910, rs3735587, rs1053275, rs17880470)	Mutation screening and case-control	Dutch/1118 sALS, 93 FALS (from 80 different families) and 1240 controls	Negative
van Blitterswijk (2012)	PON1, PON2, PON3	PON1 (rs854555, rs3917548, rs662, rs2074354, rs3917498, rs854561, rs2299260), PON2 (rs10487133, rs1639, rs2299267), PON3 (rs1053275, rs978903, rs13226149)	GWAS	Dutch/584 sALS and 7238 controls	Negative
Lee (2015)	PON1	PON1 (rs854560, rs662)	Meta-analysis	2831 ALS cases and 3123 controls	Negative
Kasperaviciute (2007)	PON1, PON2	PON1 (rs2272365, rs854568, rs3917550, rs854541, rs3917490, rs2049649, rs854572, rs757158, rs11764692, rs8491, rs854560, rs854563, rs662, rs17166818, rs3917532, rs2237584, rs2299262, rs854573, rs854546, rs2299261, rs3917538, rs854548, rs854547, rs2299260, rs3917541, rs854571, rs2237583, rs2299257, rs854569), PON2 (rs2375005, rs2299267, rs10953147, rs43037, rs2072200, rs13226149, rs11545941, rs6954345, rs11981433, rs43042, rs43040, rs12535571, rs4729189)	Case-control candidate-Gene association study	British/822 sALS and 872 controls German/579 sALS and 361 controls	Negative

ALS, amyotrophic lateral sclerosis; sALS, sporadic amyotrophic lateral sclerosis; fALS, familial amyotrophic lateral sclerosis; FTD, frontotemporal dementia; GWAS, genome-wide association study; PON1, paraoxonase 1; PON2, paraoxonase 2; PON3, paraoxonase 3; OR, odds ratio; C.I., confidence interval; NM, not mentioned.

Table 2
 Baseline characteristics of studies investigating the association between ALS risk and ALAD, VDR, SNCA, MT family, MTF-1, GSS, FMO, SOD1, HFE, Transferrin, GSTs, PGC-1 α , Nr1f2, ACHE, BCHE, NTE, FAH, CNR1, AADACL1, AFMID, APEH, CYP1A, CYP1B1, CYP2B6, CYP2C, CYP2D6, CYP2E1 and CYP3A genes.

Author (year)	Gene	Polymorphisms	Type of study	Ethnicity/participants	Main results
Kamel (2003, 2005)	ALAD, VDR	ALAD [rs1800435 (K59N)], IVS2 + 299G > A] VDR (BsmI)	Case-control candidate-gene association and gene-environment study	New England citizens-English speakers/103 ALS and 38 controls	The ALAD 2 allele was associated with increased ALS risk and decreased lead levels in patella and tibia, but not in blood IVS2 + 299G > A was associated with decreased ALS risk and decreased bone lead levels Negative results for the VDR B allele A polymorphism in delta-aminolevulinic acid dehydratase gene was associated with a 1.9-fold increase in ALS risk No association between ALAD (ALAD2 carriers VS ALAD1-1 homozygotes) and ALS Lead-ALS association was detected, among ALAD1-1 carriers (after adjustment for age and CTX) Negative
Fang (2010)	ALAD	rs1800435 (K59N)	Case-control candidate-gene association and gene-environment study	US/151 ALS and 184 controls	
Guo (2014)	SNCA	rs2736990, rs356220	Case-control	Chinese/778 sALS and 721 controls	Negative
Chen (2015)	SNCA	rs3775444, rs3822086, rs11931074	Case-control	Chinese/885 sALS and 846 controls	Negative
Morahan (2007)	MT-III	8 novel identified SNPs	Mutation screening and case-control	Australian/885 sALS and 846 controls	Genotype distribution of one SNP (A1422C) was significantly different between sALS patients and controls ($p < 0.02$)
Morahan (2007)	MT family genes, MTF-1, GSS	MT-I (rs7403881, rs2070836, rs11076161, rs7190725, rs1875233, rs2291957, rs12315, rs2301234), MT-IIa (rs1610216, rs28366003), MTF-1 (rs9660548, rs12751325, rs473279), GSS (rs3761144, rs734111, rs2236270, rs725521)	Case-control candidate-gene association and gene-environment study	European/186 sALS and 186 controls	Significant difference between sALS patients and controls in the intronic rs7403881 upstream of MT-I and haplotypes covering MT-1 isoforms Rs12751325 MTF-1 SNP differed in female sALS patients The haplotype of SNPs across GSS interacted with metals and solvents/chemicals to increase the risk of sALS.
Hayashi (2006)	MT-III, MT-IIA	MT-IIA [Promoter SNP (-5)]	Mutation screening and case-control	Japanese/37 sALS and 206 controls	Negative Detection of a novel SNP in the promoter region of MT-IIA gene but not in MT-III gene
Eum (2015)	HFE, GSTs, Transferrin	HFE [(rs1800562) (C282Y), rs1799945 (H63D)], GSTs (Ile105Val), Transferrin (TTC2)	Case-control	New England citizens-English speakers/100 sALS and 194 controls	Increased ALS risk in carriers of H63D variant allele compared to non-carriers ALS risk was found to be unaffected by C282Y, TTC2 and GSTP1 mutations H63D, C282Y, GSTP1 affected the association between lead and ALS Negative
Yen (2004)	HFE	rs1800562 (C282Y), rs1799945 (H63D)	Case-control	White, black, Asian, Hispanic for ALS cases/51 sALS and 47 controls	
Wang (2004)	HFE	rs1800562 (C282Y), rs1799945 (H63D)	Mutational screening and case-control	US (most of the patients)/121 sALS and 133 controls	Higher frequency ($p < 0.005$) of the mutated allele in ALS patients compared to controls (30.6% vs. 14.3%). All mutations were in H63D, except for one in C282Y
Goodall (2005)	HFE	rs1800562 (C282Y), rs1799945 (H63D)	Case-control	UK/379 sALS and 400 controls	

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Table 2 (continued)

Author (year)	Gene	Polymorphisms	Type of study	Ethnicity/participants	Main results
Sutedja (2007)	HFE	rs1800562 (C282Y), rs1799945 (H63D)	Retrospective study case-control candidate-gene association study, pooled analysis of previous studies	Dutch/289 sALS and 5886 controls	The H63D polymorphism was overrepresented in sALS patients (OR 1.85, 95%CI: 1.35 to 2.54) Case-control: homozygosity for H63D was associated with increased risk of ALS (OR), 2.2; 95%CI, 1.1–4.1) Pooled-analysis: positive association between H63D homozygotes, heterozygotes and mutation carriers [(OR, 2.7; 95% CI, 1.7–4.4), (OR, 1.5; 95% CI, 1.0–2.1) and (OR, 1.7; 95% CI, 1.1–2.5), respectively] In ALS patients, heterozygosity for H63D was associated with higher age of onset Higher frequency of the mutated allele H63D in ALS patients compared to controls (28.8% v 14.8%; OR 2.25, 95%CI 1.30–3.93 and $p = 0.004$) Increased frequency of the combination of the three mutations in the ALS group (33.3% v 17.3%; $p = 0.002$). Heterozygosity for H63D was significantly related to sALS (OR 3.10, 95%CI: 1.49–6.47, $p = 0.002$) A difference in C282Y between patients and controls Low frequency of Y allele in sALS group compared to controls Negative
Restango (2007)	HFE	rs1800562 (C282Y), rs1799945 (H63D), S65C	Case-control	Italians/149 sALS and 168 controls	
He (2011)	HFE	rs1799945 (H63D)	Case-control	Chinese/195 sALS and 405 controls	
Praline (2012)	HFE	rs1800562 (C282Y), rs1799945 (H63D)	Case-control	French/824 sALS and 583 controls	
van Rheenen (2013)	HFE	rs1799945 (H63D)	Case-control and a meta-analysis	Case-control study: Europeans/3962 sALS and 5072 controls Meta-analysis: Multiethnic/5894 sALS and 12,379 controls	
Su (2013)	HFE	rs1799945 (H63D)	Case-only study	Caucasian/22 sALS with WT HFE and 16 sALS either HT or MT for H63D HFE	Longer average disease duration and lower muscle SOD1 protein in ALS patients with H63D HFE compared to ALS patients with wild-type HFE.
Li (2014)	HFE	rs1800562 (C282Y), rs1799945 (H63D)	Meta-analysis	C282Y:1692 cases and 8359 controls/ H63D:5849 cases and 13,710 controls	C282Y polymorphism was significantly associated with decreased ALS risk in the allele model (Y vs C: OR = 0.76, 95%CI = 0.62–0.92, $p = 0.005$) and in the dominant model (YY + CY vs CC: OR = 0.75, 95%CI = 0.61–0.92, $p = 0.006$) Negative
Chio (2015)	HFE	rs1799945 (H63D)	Case-control	Italians/1119 ALS and 1032 controls Sardinians/232 ALS and 121 controls	
Siddons (1996)	CYP2D6	CYP2D6(B) [G to A transition], CYP2D6(A) [BP del (exon 5)], CYP2D6(T)[BP del (exon 3)]	Case-control	50 ALS, 13 ALS + FTD and 720 controls	Increased frequency of the CYP2D6(B) allele in ALS patients ($p = 0.006$). Higher frequency of both SNPs in the female sALS group compared to controls ($p < 0.01$)
Cereda (2006)	FMO	(g. + 27,568), (g. + 27,664)	Case-control	Italians/78 sALS and 90 controls	

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Table 2 (continued)

Author (year)	Gene	Polymorphisms	Type of study	Ethnicity/participants	Main results
Kasperavectute (2007)	ACHE, BCHE, NTE, FAH, CNR1, AADACL1, AFMD, APEH, CYP1A, CYP1B1, CYP2B6, CYP2C, CYP2D6, CYP2E1, CYP3A, MT3	ACHE (rs6942607, rs3757868, rs7636, rs13241786), BCHE (rs4680664, rs2686410, rs9873779, rs9838443, rs9883728), CNR1 (rs1511973, rs1192572, rs4639017, rs1799807, rs1803274, rs1464026), NTE (rs526411, rs540516, rs10418152, rs644053, rs591040, rs492092, rs7250311, rs7260296, rs612862, rs2446181, rs586551, rs507814), AFMD (rs501580, rs2446182), FAH (rs6703669, rs932816, rs324420, rs12029329, rs324419, rs11576941, rs324425, rs3766246), CNR1 (rs806368, rs806380, rs6454672, rs806378, rs7766029, rs806374, rs1049353, rs806375), rs806369, rs806377, rs806365), AADACL1 (rs9883329, rs492748, rs6445072, rs497316, rs13080424), rs6771424, rs733023, rs2901811, rs6778941, rs1799598, rs559995, rs662271, rs1522354, rs6796724, rs3932352, rs488304, rs1105152, rs10804847, rs9827009, rs9829555, rs234015, rs17524770, rs234012, rs483772, rs170883, rs484753, rs234000, rs2302815, rs234016, rs669376, rs2302816), AFMD (rs744120, rs8072874, rs3764383, rs8082142, rs3764384, rs7221585, rs12450989, rs2854704, rs16970907), APEH (rs9823546, rs1131095, rs4855881), CYP1A (rs2470893, rs4646421, rs762551, rs11854147), CYP1B1 (rs162555, rs163078, rs162556, rs1056836, rs2256327, rs9341250, rs9341246), CYP2B6 (rs12721645, rs3745274, rs8192712, rs8192709, rs4803417, rs11673270, rs1042389, rs11666982, rs8100458, rs10425769), CYP2C (rs4244285, rs1322179, rs4986894, rs2281891, rs10509681, rs17110453, rs1113129, rs9332197, rs1010570, rs2298037, rs2475377, rs11572181, rs1934967, rs2253635, rs2860968, rs1934953, rs12778431, rs1934954, rs1188147, rs4917639, rs1058930, rs7909236, rs2860840, rs1322181, rs2275620, rs12249418, rs7896133, rs7099637, rs9332214, rs9332239, rs1057910, rs9332103, rs9332130, rs2017319, rs11572080), CYP2D6 (rs11090076, rs5758589), CYP2E1 (rs7092584, rs915906, rs10776687), rs2515641, rs2070673, rs6413420, rs9418990, rs915908), CYP3A (rs12333983, rs776746, rs4646450, rs4646437, rs2687134, rs17161780, rs4986910, rs12721627), MT3 (rs9938618, rs12444489, rs410155, rs4784693, rs7186103)	Case-control	British/822 sALS and 872 controls German/579 sALS and 361 controls	Negative
Pasquinelli (2016)	PGC-1α	Gly4825er	Case-control	Caucasians/197 sALS and 197 controls	Negative
LoGerfo (2014)	Nrf2 promoter	−653 A/G, −651 G/A, and −617C/A	Case-control	Italians/145 sALS and 73 controls	Negative
Broom (2004)	SOD1	−3392, +2811, +6782, +18,636 and a deletion spanning	Case-control	Europeans/233 sALS and 248 controls	Negative

ALS, amyotrophic lateral sclerosis; sALS, sporadic amyotrophic lateral sclerosis; fALS, familial amyotrophic lateral sclerosis; FTD, frontotemporal dementia; GWAS, genome-wide association study; MT, metlothionein; MTF-1, metal transcription factor-1; GSS, glutathione synthetase; CYP, cytochrome P450; SNCA, alpha-synuclein; GST, glutathione S-transferase; HFE, hemochromatosis; FMO, Flavin-containing monooxygenases; CTX, C-terminal telopeptides of type I collagen; HFE, hemochromatosis; SOD1, superoxide dismutase 1; ACHC, acetylcholinesterase; BCHE, butyrylcholinesterase; NTE, Neurotrophin Target Esterase; FAH, fumarylacetoacetate hydrolase; CNR1, cannabinoid receptor type 1; AADACL1, arylacetamide deacetylase-Like 1; AFMD, arylformamidase; APEH, acylaminoacyl-peptide hydrolase; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Nrf2, nuclear factor erythroid-derived 2-like 2; OR, odds ratio; C.I., confidence interval.

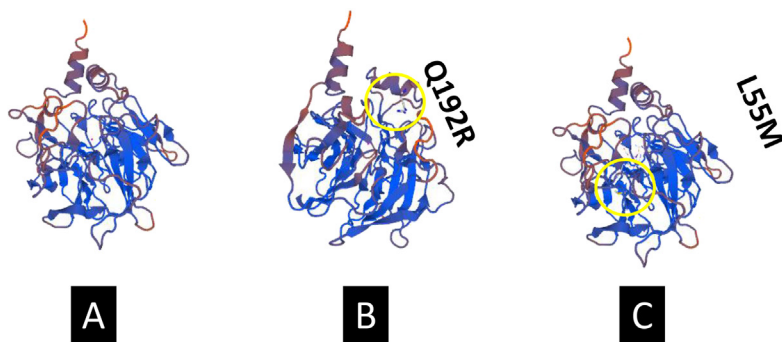
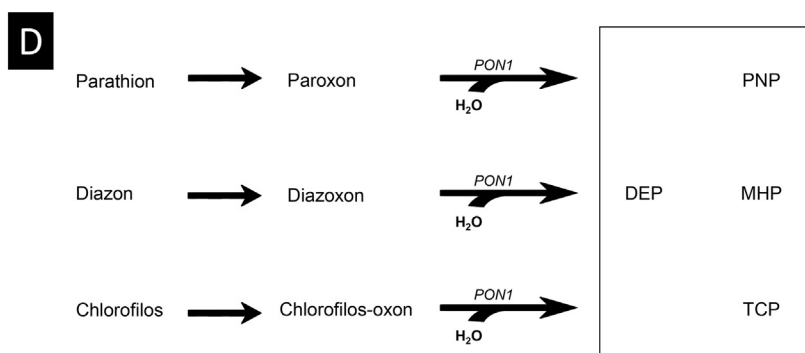


Fig. 1. A. The 3D model of the normal PON1 protein; B. The 3D model of the mutant Q192R PON1 protein; C. The 3D model of the mutant L55M PON1 protein; D. Parathion, diazinon and chlorpyrifos are oxidized by liver's cytochrome P450 to their corresponding oxons. Paraoxonase 1 (PON1) catalyzes the hydrolysis (detoxification) of these products, leading to the metabolites: diethylphosphate (DEP), para-nitrophenol (PNP), methylpyrimidinol (MHP) and trichloropyridinol (TCP). Variants across PON1 gene influence the concentration of paraoxonase-1 enzyme in the serum, the protein stability and its catalytic activity, resulting in defective detoxification.



and 49 from rural areas) (Diekstra et al., 2009). Significant association for L55M, (rs854560) and also a weaker signal from Q192R (rs662) were observed. The R192/L55 haplotype was underrepresented in rural residents (Diekstra et al., 2009). Finally, in the rural group, increased load of M allele of L55M was associated with decreased survival (Diekstra et al., 2009).

In contrast to the limited number of studies with gene-environment interaction design, quite a few case-control studies have examined the role of PON1 variants in sALS. In a study of 166 Polish Caucasians patients with sALS, the genotype with R allele of rs662 was significantly associated with sALS (Slowik et al., 2006). Moreover, rs854560 PON1 was found to be associated with sALS in the Irish population (Cronin et al., 2007). Finally, in a cohort consisted of UK and US sALS patients, rs2074351 and rs705382 as well as 5-SNP haplotypes (rs854565/rs2299261/rs705381/rs705382/rs4141217) were associated with sALS (Landers et al., 2008).

In contrast to the previous findings, there are also negative reports concerning the association between the previously referred PON1 polymorphism and sALS. SNPs across PON1 failed to show evidence about in North American, French, Canadian, Swedish, English, Italian, Chinese, Polish, Dutch, British, German cohorts (Chen et al., 2012a; Kasperaviciute et al., 2007; Ricci et al., 2011; Saeed et al., 2006; Valdmanis et al., 2008; van Blitterswijk et al., 2012; Zawislak et al., 2010). Furthermore, two meta-analyses have revealed negative results (Lee et al., 2015; Wills et al., 2009). (Lee et al., 2015). In view of the previous results, the role of PON1 gene in sALS remains uncertain. However, the strongest indication exists for rs854560 (L55M), rs662(Q192R), rs2074351 and rs705382.

Paraoxonase-2 and paraoxonase-3 genes: PON2 and PON3 enzymes metabolize oxidized lipids and protect against lipid peroxidation. They are not involved though in organophosphate metabolism, like PON1 enzyme (Ng et al., 2001; Reddy et al., 2001; Wills et al., 2009). The risk alleles of the non-synonymous coding PON2 polymorphisms rs6954345 and rs12026 have been associated with lower PON activity (Cronin et al., 2007). The possibility that individuals carrying the C allele of the

PON2 C311S polymorphism may be more susceptible to ALS was tested in a case-control study of Polish population, revealing an association between the C allele and sALS in dominant and additive models (Slowik et al., 2006). However, the S allele has also been found to confer susceptibility to neurodegeneration, as the SS genotype of the S311C PON2 polymorphism (SS genotype) has been associated with the risk of AD in a recent meta-analysis (Nie et al., 2017). Moreover, the intronic variants rs10487132 (PON3) and rs11981433 (PON2), were associated with sALS in the trio model (parents-affected child triad). Specifically, rs10487132 was associated with sALS in 450 nuclear pedigrees, comprising trios and discordant sibpairs (Saeed et al., 2006). Rs10487132 (PON3) has been reported to be associated with sALS in a cohort consisting of 166 Irish sALS patients and 437 controls (Cronin et al., 2007). However, PON2 and PON3 variants failed to reach any statistical significance in case-control models, in several cohorts (Chen et al., 2012a; Chen et al., 2012b; Kasperaviciute et al., 2007; Ricci et al., 2011; Saeed et al., 2006; van Blitterswijk et al., 2012). Rs978903 (PON3) and rs11981433 (PON2) have also been meta-analyzed by Willis et al. revealing negative association with ALS (Willis et al., 2009). The culture of null hypothesis significance testing may be considered as a factor for the lack of reproducibility of the positive results (Lash, 2017).

Haplotypes of SNPs of PON1, PON2 and PON3 have also been examined. Cronin et al. reported significant association between sALS and the haplotype of the risk alleles of rs854560 (PON1) and rs10487132 (PON3) in an Irish population. Significant association was also reported between sALS and the haplotype of the alleles of rs854560 (PON1), rs705381 (PON1) and rs10487132 (PON3) (Cronin et al., 2007). Additionally, the R-C haplotype, consisting of the R allele of rs662 (PON1) and the C of C3111S (PON2) was overrepresented among polish sALS patients (Slowik et al., 2006). It is possible that each SNP may confer partial susceptibility to ALS development, possibly, under gene to gene interaction with other polymorphisms across PON1, PON2 and PON3 genes.

3.2. ALAD and VDR

The d-aminolevulinic acid dehydratase (ALAD) enzyme, which is also known as porphobilinogen synthase, is mainly expressed in liver and erythrocytes (Wetmur, 1994). The main function of this enzyme is to catalyze the second step in heme synthesis, by adding two molecules of aminolevulinic acid. In this way, a precursor of heme, cobalamins-monopyrrole-porphobilinogen, is synthesized (Jaffe, 2000). The ALAD gene seems to influence the toxicokinetics of lead. The non-synonymous coding polymorphism, K59N (G177C), results from the substitution of G with C dinucleotide, at the coding position 177. This leads to the conversion of lysine (K) into asparagine (N), creating the ALAD 2 variant allele, which is opposite to the ALAD 1 wild type allele (Wetmur, 1994). The ALAD-2 protein has been associated with lead levels, lower in the bones and higher in the blood (Kelada et al., 2001). Due to higher electronegativity, it enchains lead tighter than the less electronegative ALAD 1 protein (Bergdahl et al., 1997). This could alter the toxicokinetics of lead, especially among high-dose populations, leading to longer abidance of lead in blood and tissues (Kelada et al., 2001). The subsequent toxic effect results by two ways; either from the longer effect of lead; or from the abundant accumulation of aminolevulinic acid, due to ALAD inhibition (Kelada et al., 2001).

Fang et al. recruited 184 ALS cases and 194 controls of US veterans and performed a case-control study of gene-environment interaction. They mainly focused on K59N polymorphism and blood lead levels. In addition to blood lead measurements, the authors also measured plasma biomarkers of bone formation [procollagen type 1 amino-terminal peptide (PINP)] and resorption [C-terminal telopeptides of type 1 collagen (CTX)]. No association between ALAD (ALAD2 carriers VS ALAD1-1 homozygotes) and ALS was revealed, apart from ALAD1-1 carriers after adjustment for age and CTX (Fang et al., 2010). On the contrary, another case-control study of gene-environment interaction, with 109 ALS patients and 256 controls, showed a relationship between ALS and ALAD 2 allele. Blood and bone (patella and tibia) lead levels were measured. Specifically, the ALAD 2 allele was associated with decreased levels of lead in patella and tibia but appeared to be unrelated to blood lead levels (Kamel et al., 2005; Kamel et al., 2003). Moreover, the authors identified IVS2 + 299G > A, a previously unreported polymorphism at the Msp1 site in intron 2. This polymorphism was associated with a significant decrease in bone lead levels and ALS risk (Kamel et al., 2003).

Vitamin D may affect absorption and distribution of lead (Fullmer, 1992). The vitamin D receptor (VDR) gene encodes the vitamin D receptor protein. The BB genotype of the intronic BsmI polymorphism between exons 8 and 9 may influence calcium absorption and distribution (Zmuda et al., 2000). Consequently, the BB genotype may affect lead toxicity (Kamel et al., 2003). However, it is rather unlikely that an intronic polymorphism, such as BsmI, represents a functional loci across VDR gene (Zmuda et al., 2000). Therefore, the coexistence of a proximal exonic SNP, high lead dose and BsmI polymorphism, may lead to defective VDR function (Fang et al., 2010). However, Kamel et al. reported negative results concerning BsmI and its effect on lead levels and/or ALS development (Kamel et al., 2003).

The FokI functional VDR polymorphism has been associated with PD and with the cognitive decline in PD (Gatto et al., 2016; Lee et al., 2014; Niu et al., 2015). ApaI, BsmI, and TaqI polymorphisms have not been associated with susceptibility to PD (Lee et al., 2014; Niu et al., 2015). Furthermore, associations between VDR polymorphisms (TaqI and ApaI) and AD susceptibility have been reported (Laczanski et al., 2015; Lee et al., 2014), depending though on ethnicity and climatic conditions (Laczanski et al., 2015). The possible existence of gene-environment interactions may explain, to some degree, the lack of association (Kang et al., 2016). Therefore, despite the lack of association between VDR SNPs and ALS, there is some indication for their contribution to neurodegeneration.

3.3. SNCA

SNCA constitutes a major component of pathological features in PD and MSA, such as Lewy bodies, neurites and glial cytoplasmic inclusions (Mollenhauer et al., 2011; Wakabayashi et al., 1998). It is also considered to be a risk factor for these diseases (Al-Chalabi et al., 2009; Xiromerisiou et al., 2010). There is evidence of overlapping clinical phenotypes among PD, ALS, and MSA, suggesting that SNCA may confer susceptibility to ALS (Guo et al., 2014). Moreover, pesticides expedite the rate of a-syn fibrillation. PD animal models with a transgenic a-syn, revealed increased a-syn pathology, when exposed to pesticides (Gao and Hong, 2011; Uversky et al., 2001). Therefore, SNCA may influence the risk of ALS by affecting neuronal toxicity, under combined interaction with pesticides. In total, 5 SNPs across SNCA have been examined, up to now (rs2736990, rs356220, s3775444, rs3822086 and rs11931074) (Guo et al., 2014) producing negative results (Chen et al., 2015; Guo et al., 2014).

Previous studies examining the interaction between REP1 SNCA polymorphism and pesticide exposure in PD etiology, yielded little evidence of an involvement as risk factors or as effect modifiers. These studies though limited by small sample size or assessment of pesticide exposure (Brighina et al., 2008; Gatto et al., 2010). Also, GG genotype of rs10516846 across SNCA gene, may be associated with an increased risk of AD and elevated SNCA level in CSF (Wang et al., 2016). Therefore, the overall contribution of SNCA SNPs to neurodegeneration seems unlikely.

3.4. MT family genes, MTF-1, GSS

Metallothioneins (MTs) are a family of metal (Cu/Zn)-binding proteins. Metallothionein-I (MT-I) and metallothionein-II (MT-II) are present in all human tissues, while Metallothionein-III (MT-III) mainly exists in the central nervous system and metallothionein-IV in the stratified squamous epithelia (Thirumoorthy et al., 2011). The Metallothionein (MT) family is implicated in heavy metal detoxification pathways. Lack of MT-I and MT-II is associated with increased heavy metal toxicity (Liu et al., 1995), while overexpression of MT seems to have a protective role (Klaassen and Liu, 1998). Deficiencies in MT isoforms may also influence the cellular defensive mechanisms against heavy metals, as MTs increase the cellular export and reduce the cellular uptake of heavy metals. They accomplish these procedures through sequestration of free toxic metal in the cell (Morahan et al., 2007a). Metal transcription factor-1 (MTF-1) influences MT gene expression related to heavy metals and, consequently, the damage of motor neurons (Gunther et al., 2012; Morahan et al., 2007c). Glutathione is possibly involved in the detoxification mechanisms regarding pesticides and heavy metals (Abel et al., 2004; Jozefczak et al., 2012).

One case-control study with gene-environment interaction examined the possibility that individuals carrying specific MT, MTF-1 and GSS polymorphisms, may be more vulnerable to ALS development. The sample consisted of 186 sALS and 186 controls with European ancestry (Morahan et al., 2007c). *MT-I Isoforms*: C allele and C/C genotype of M1 isoform were reported to be more frequent in all sALS patients and even more frequent in the male sALS subgroup. Additionally, M1C/C genotype was found to increase the risk of sALS, while M5 A/A genotype revealed a protective effect. The most common haplotype, CGGGGGGG, which was constructed by the examined MT-I SNPs, was more frequent in the sALS group (26%) compared to controls (18%) ($p = 0.032$). Also, the GGAGAGGG haplotype was more frequent in controls (12%) than in the sALS group (7%). When the M1 SNP was included in the analysis, the haplotype difference between the groups was found to be stronger ($p = 0.019$ vs $p = 0.026$). Also, the GAG haplotype of M2-M4 SNPs had a decreased frequency in the sALS group. The subsequent analysis for gene-environment interactions yielded negative results (Morahan et al., 2007c). *MT-IIa gene*: no significant association was revealed. *MTF-1*

gene: F2 MTF-1 C allele, C/C and C/T genotypes were more common in female sALS patients but not in the total patients or in the male sALS group, compared to controls. Only rare haplotypes (frequency < 2%) differed significantly between patients and controls. Therefore, the authors suggested that it is rather unlikely to expose biological effects. *GSS gene*: GSS genotype–metal interactions differed between sALS patients and healthy individuals. Moreover, an association was reported between the GCGC haplotype and sALS, when patients exposed to metal were compared to those exposed to solvents/chemicals. Neither an association trend nor interactions were observed for herbicide/pesticide exposure (Morahan et al., 2007c).

Morahan et al., after the identification of eight novel SNPs in the 5' untranslated region and in the intron 2 of MT3, performed a case-control study. Despite the significant difference in the genotype distribution of the SNP (A1422C) between sALS and controls, the authors suggested that this association might not be biologically relevant. They concluded that the variants of MT3 gene are unlikely to be responsible for susceptibility to sALS (Morahan et al., 2005; Morahan et al., 2007c). They were also interested in examining differences in methylation levels of the CpG islands of MT-Ia and MT-IIa isoforms, between sALS patients and controls. However no significant divergence was observed (Morahan et al., 2007a).

Hayasi et al. screened 37 Japanese sALS and 206 sex-matched healthy controls for mutations across MT-IIA promoter and MT-III genes. Only the novel A/G SNP (–5) on MT-IIA promoter was detected. However, it is rather unlikely for this SNP to influence the clinical type, the progression rate or the age of onset (Hayashi et al., 2006). Kasperavičiute et al. have also reported negative results, regarding the role of MT-III gene polymorphisms in sALS (Kasperavičiute et al., 2007).

3.5. FMO

Flavin-containing monooxygenase (FMO) proteins belong to the family of microsomal enzymes catalyzing the oxidation of several endogenous and exogenous factors, including drugs (Cashman, 2000). Additionally, yeast FMO (yFMO) is involved in redox balance, by catalyzing the oxidation of biological thiols, such as the oxidation of reduced glutathione (GSH) to glutathione disulfide (GSSG) (Cereda et al., 2006; Suh et al., 2000). Mutated alleles of two SNPs on the 3-UTR of FMO gene (g. +27,568) and (g. +27,664) have been found to influence together the sALS risk. However, interdependent action of them and the gender specific effect cannot be excluded (Cereda et al., 2006).

3.6. SOD1, HFE, Transferrin, GSTs, PGC-1α and Nrf2

Oxidative stress contributes to the neurodegenerative process of neurological disorders, including ALS (Cookson and Shaw, 1999; Dardiotis et al., 2013a). Cu,Zn superoxide dismutase (SOD1) is the first identified genetic risk factor for approximately 20% of familial and 3% of sporadic ALS cases (Hayashi et al., 2016). Several pathophysiological mechanisms, regarding the implication of SOD1 to ALS, have been proposed, including oxidative stress, mitochondrial dysfunction and excitotoxicity (Hayashi et al., 2016). Broom et al. recruited 233 sALS cases and 248 healthy controls and genotyped them for four SNPs (–3392, +2811, +6782, +18,636) and for deletion spanning across SOD1 gene (Broom et al., 2004). However, they did not confirm any connection between polymorphisms or their haplotypes and sALS susceptibility, age of onset, survival, and site of onset (Broom et al., 2004).

The G allele of the rs2070424 SOD1 polymorphism appeared to have a protective role against AD in a Polish study (Spisak et al., 2014).

Oxidative stress is also influenced by iron accumulation. Defective iron homeostasis is associated with oxidative damage (Wang et al., 2004). Iron related genes may either cause or predispose to dopaminergic cell damage, possibly due to the contribution of iron to the synthesis of tyrosine hydroxylase (Snyder and Connor, 2009). Mutations in the Hfe gene are associated with hemochromatosis, a disease

that is characterized by iron overload (Hanson et al., 2001). Therefore, the Hfe variants could be implicated to ALS pathophysiology, through metal-mediated oxidative stress (Wang et al., 2004). H63D polymorphism across HFE gene was found to accelerate the progression of ALS in SOD1 transgenic mice (Nandar et al., 2014). Moreover, SOD1 ALS patients, carrying the risk G allele of H63D, had a significantly longer survival compared to those with the wild type genotype (Chio et al., 2015). Additionally, sALS patients, homozygotes or heterozygotes for H63D mutant allele, were reported to have 28.1 months longer average disease duration and 39.3% lower muscle SOD1 protein compared to homozygotes for the wild type allele (Su et al., 2013). Transferrin is a transmembrane iron-transport glycoprotein that binds to iron tightly and reversibly. The rs1049296 polymorphism across transferrin has been associated with increased PD and AD risk (Rhodes et al., 2014; Wang et al., 2013). Transferrin also interacts with HFE (Namekata et al., 1997). GSTO1 and 2 are members of the GST family and they are abundant in the whole human body, but less in the brain (Wang et al., 2005). They influence the reduction of oxidative stress, through glutathione-dependent detoxification (Van De Giessen et al., 2008). Rs4925 (Ala140Asp) is a functional SNP decreasing thioltransferase activity of the wild-type GSTO1 (Tanaka-Kagawa et al., 2003). Several SNPs have been associated with age of fALS onset. However, this association was evident only in a Swedish cohort. Possibly, the reported marginal trends could imply that variations across GST genes may be phenotypically evident in certain ethnic groups (Van De Giessen et al., 2008).

Quite a few case-control studies have been conducted examining the role of HFE polymorphisms in sALS. Higher frequency of the mutated allele was revealed in ALS patients than in controls. Moreover, H63D or C282Y mutations were associated with a decrease in h-actin, α-tubulin and Cu/Zn-SOD1 expression compared to wild types, thus indicating alterations in axonal transport (Wang et al., 2004). H63D polymorphism was overrepresented in sporadic ALS individuals (Goodall et al., 2005). Increased risk of ALS was also revealed in an Italian population with sALS, resulting from H63D risk allele, as well as from the combination of C282Y, H63D and S65C risk alleles (Restagno et al., 2007). Dutch homozygotes for H63D revealed an increased risk for developing ALS (Sutedja et al., 2007). Heterozygosity for H63D was significantly related to sALS in a Chinese cohort (He et al., 2011). Additionally, a lower frequency of the Y allele of C282Y was reported in a French sALS group compared to controls (Praline et al., 2012). Carriers of the H63D variant allele had increased risk for ALS compared to non-carriers, but the ALS risk seems to be independent of C282Y, Tfc2 and GSTP1 mutations. Moreover, H63D was noted to affect patella and tibia lead levels, associated with ALS. Specifically, in sALS patients, C282Y was associated with patella and tibia lead levels, while GSTP1 was related to blood lead levels (Eum et al., 2015). Additionally, there is strong evidence that H63D polymorphism has a protective role against AD risk (Lin et al., 2012), while there is only mild indication that the C282Y polymorphism protects against PD (Duan et al., 2016; Xia et al., 2015).

Negative results have also been reported for both C282Y and H63D (van Rheenen et al., 2013; Yen et al., 2004). Additionally, two meta-analyses have been performed so far, concerning FHE SNPs and ALS. The first one revealed negative correlation (van Rheenen et al., 2013). On the contrary, the second and most recent one yielded a significant OR for C282Y polymorphism. More precisely, C282Y was significantly associated with decreased ALS risk, in a specific allele model (Y vs C: OR = 0.76, 95%CI = 0.62–0.92, $p = 0.005$) and also in the dominant model of this allele (YY + CY vs CC: OR = 0.75, 95%CI = 0.61–0.92, $p = 0.006$) (Li et al., 2014). Results from pooled-analysis suggested a positive association between ALS and H63D homozygotes, heterozygotes and mutation carriers. Moreover, an association between heterozygosity for H63D and a higher age of onset was observed in ALS patients (Sutedja et al., 2007).

Peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-

1α), consists a transcriptional co-activator, which mainly regulates mitochondrial biogenesis and contributes to antioxidant defense mechanisms (Qi et al., 2015). Gly482Ser SNP has been associated with a decreased gene expression and a reduction in the activity of PCG-1α (Prior et al., 2012). ALS carriers of the Gly482Ser polymorphism show increased exercise-related oxidative stress, despite the lack of strong evidence of association between Gly482Ser and ALS (Pasquinelli et al., 2016). The intracellular redox balance is also influenced from the nuclear factor erythroid-derived 2-like 2 (NFE2L2/Nrf2) pathways. However, −653A/G, −651G/A, and −617C/A SNPs across the Nrf2 gene promoter, which had previously been reported to have functional significance and/or influence on basal Nrf2 expression and function, did not reveal any association with increased ALS risk (LoGerfo et al., 2014; Marzec et al., 2007).

3.7. Other genes

Several variants across CYP2D6 gene were reported to influence the expression and activity of CYP2D enzyme and, consequently, the metabolism of xenobiotics. Organophosphate compounds, triazine (atrazine), carbamates (carbaryl, maneb, ziram) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are metabolized to some degree by the cytochrome (CYP) P450 enzyme CYP2D6 (Neafsey et al., 2009; Zhou, 2009). Rs389209 [CYP2D6*4 (G > A)] polymorphism may represent a variant with a significant functional effect. More specifically, homozygotes for A allele revealed defective CYP2D6 activity, compared to those with AG and GG genotypes. Moreover, this SNP is responsible for aberrant mRNA splicing at intron3/exon4 boundary, causing an early termination (Dardiotis et al., 2013b; Gough et al., 1990).

Sibbons et al. examined the following polymorphisms: CYP2D6(B) [G to A transition], CYP2D6(A) [BP del (exon 5)], CYP2D6(T)[BP del (exon 3)]. They detected an increased frequency of CYP2D6 (B) allele in ALS patients (Siddons et al., 1996). Kasperveciute et al., examined quite a few polymorphisms across CYP1A, CYP1B1, CYP2B6, CYP2C, CYP2D6, CYP2E1 and CYP3A for possible connection with sALS. The results of this study, however, failed to reach any statistical significant threshold among British and German cohorts (Kasperveciute et al., 2007). In the same study, authors also analyzed a few additional genes that are involved in xenobiotic metabolism pathways [PON1, PON2 and MT3, which are described in the corresponding sections, as well as acetylcholinesterase (ACHE), butyrylcholinesterase (BCHE), Neuro-pathy Target Esterase (NTE), fumarylacetoacetate hydrolase (FAH), cannabinoid receptor type 1 (CNR1), arylacetamide deacetylase-Like 1 (AADACL1), arylformamidase (AFMID) and acylaminoacyl-peptide hydrolase (APEH)], showing negative results (Kasperveciute et al., 2007).

4. Concluding remarks

Both genetic and environmental factors are supposed to increase susceptibility to ALS development. Unfortunately, there are a relatively small number of studies examining the interactions between genetic and environmental factors. It is also evident that each determinant may have a minor effect on ALS risk. In view of the former evidence, studies estimating the combined effect and the interactions between genetic and environmental factors are more likely to detect relevant associations, than analyze them separately.

Human genetic association studies examining the interaction between genes and pesticides or metal exposure, on the risk of ALS, have provided remarkable results. More precisely, based on our results, PON1 [rs854560(L55M), rs662(Q192R), rs2074351 and rs705382], PON2 (C311S, rs11981433) and PON3 (rs10487132) seem to be the most significant genes that are implicated in pesticides metabolism and possibly influence ALS development. As far as the genetic variants that are implicated in lead toxicity are concerned, the strongest indications derived from ALAD [rs1800435 (K59N), IVS2 + 299G > A] and VDR

(BsmI) variants. Finally, a few evidence exist for MT-III (A1422C), MT-I (upstream rs7403881) and GSS, which are implicated in heavy metal detoxification pathways, as well as for HFE [rs1800562 (C282Y), rs1799945 (H63D)] genes that possibly affect oxidative stress and, consequently, iron accumulation. Of note, genetic association studies examining the interaction between genes and pesticides or metal exposure, have also revealed associations with other neurological diseases (AD, PD, MS and IS). The majority of them concerned AD and PD, suggesting an overall effect and interaction between polymorphisms implicated in detoxification pathways and neurodegeneration.

Among the environmental toxicants, pesticides appear to be the strongest risk factors for ALS. Milder indications, though, exist for heavy metals, mercury, selenium, mercury, cadmium, iron, lead and xenobiotics. Therefore, both toxicants themselves, and genetic variability that influences these metabolic pathways, appear to interact to increase susceptibility for ALS. However, studies examining the role of both toxicants and genetic variability as ALS risk factors, and their interactions, are relatively few. In view of the former considerations, definitive conclusions whether toxicants are the primary cause and the genes are additional factors for ALS development, or vice versa, cannot be drawn so far.

It has been indicated that genetic susceptibility, either in pesticide metabolism or in heavy metal detoxification pathways and toxicokinetics of lead, may increase the risk of ALS development. However, this indication is limited and uncertain at the present. The culture of null hypothesis significance testing may be considered as a factor for the lack of reproducibility of the positive results (Lash, 2017). By correct use and interpretation of statistical value, the misinterpretation of *p*-values, confidence intervals and statistical tests in general, could be avoided (Greenland, 2017). The scientific reasoning could not be substitute from single statistical value, index or test (Rothman, 2016; Wasserstein and Lazar, 2016). Therefore, it is of great necessity more studies with gene-environment interaction design, and studies investigating the etiologic role of assuming both environmental and genetic factors have to be conducted in the future, in order for the pathogenic mechanisms of ALS to be elucidated.

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