Environment International 116 (2018) 122–135

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

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

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ARTICLE INFO

Handling Editor: Robert Letcher

Keywords:
Amyotrophic lateral sclerosis
Pesticides
Heavy-metals
Gene-environmental interaction
SNPs

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;

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https://doi.org/10.1016/j.envint.2018.04.008
Received 12 January 2018; Received in revised form 3 April 2018; Accepted 5 April 2018

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 Capozzela 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 (Kasperaviciute 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-1α, 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, diazozon 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://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 no-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