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EARLY LIFE ENVIRONMENTAL HEALTH (J SUNYER, SECTION EDITOR)

Effect of Gene-Mercury Interactions on Mercury Toxicokinetics and Neurotoxicity

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Abstract Individuals differ in susceptibility to mercury neurotoxicity, in part, due to underlying genetic differences. This review aims to evaluate the state-of-the-art of the effect of (1) genetics on mercury toxicokinetics and (2) gene-mercury interactions on neurodevelopment and neurotoxicity. We conducted a PubMed search in September 2014 and retrieved 14 studies on the influence of genetics on mercury toxicokinetics and ten on neurological effects of gene-mercury interactions. Genes frequently studied for their influence on mercury toxicokinetics were mainly related to the metabolism of glutathione, but the results were contradictory for most of the genes. The gene-mercury interactions on child neurodevelopment and adult neurotoxicity reported were too few to draw any definite conclusion. So far, candidate gene approaches have not identified any major gene/s modifying the kinetics or toxicity of mercury, suggesting that these might be polygenic traits. More research is highly warranted to clarify if there are vulnerable subgroups to mercury neurotoxicity in humans.

Keywords *ABCC2* · *APOE* · *BDNF* · Cognitive · *GCLM* · Glutathione

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Introduction

Mercury is a ubiquitous environmental toxicant that derives both from natural sources and human activity. It can exist under several forms: elemental, inorganic, and organic; where the organic form, in particular methylmercury (MeHg), is the greatest cause of concern due to its irreversible neurotoxic effects early in life [1, 2]. Most MeHg originates in aquatic systems where it is formed from the inorganic form through the action of bacteria present in water and sediments [3]. Consumption of marine species is currently considered the major source of human exposure, and predatory fish such as swordfish and shark have the highest concentrations of MeHg [4, 5]. For inorganic (IHg) or elemental mercury, the main exposure sources are from some occupational activities and dental amalgams [6]. The occupational exposure to IHg has been well documented in gold miners [7], chloralkali workers [8], and dental professionals [9].

MeHg crosses the placenta and blood–brain barrier, and may affect critical neurodevelopmental processes including cell proliferation, migration, differentiation, synaptogenesis,

myelination, and apoptosis [10]. Children and fetuses are especially vulnerable, since their brain, immune system, and detoxification mechanisms are being developed [11, 12]. Epidemiological studies have been conducted in fish-eating populations in order to evaluate the consequences of prenatal or early life exposure to MeHg on the cognitive development; however, the results have been conflicting [13–16]. A few cross-sectional studies of low-level MeHg exposure in adults and neurologic effects have been performed, and the results have been contradictory as well [15]. Neurotoxicity associated with exposure to IHg has mainly been studied in highly exposed populations. Long-term exposure to IHg was associated with tremor and abnormal motor function in chloralkali workers [8], as well as decreased peripheral nerve function in dental professionals [9], but only some of the IHg-exposed workers developed neurotoxicity.

The lack of homogeneity for the effect of MeHg and IHg in different study populations or between individuals could be explained by several biological and non-biological factors affecting both exposure and toxicity to mercury (e.g., for MeHg toxicity, the content of beneficial nutrients from fish such as selenium or fatty acids, or co-exposure to other contaminants probably matters) [17]. A further component is the underlying genetic background that might modify mercury uptake, biotransformation, distribution, and elimination, and in turn, determines the active dose [18] (Fig. 1a).

An expert committee of the U.S. National Research Council (2000) concluded that 3 % of neurodevelopmental disorders may be a direct result of exposure to environmental toxins, and up to 25 % would be the result of the interaction between exposure to environmental toxicants and individual susceptibility genes [19]. Recently, there has been an increase in the identification of genetic variants involved in cognitive disorders [20, 21], which might also play a role in the relationship between mercury exposure and neurodevelopment and neurotoxicity.

The purpose of this review was to evaluate the state-of-the-art of the effect of (1) genetics on mercury (both IHg and MeHg) toxicokinetics and (2) gene-mercury (both IHg and MeHg) interactions on child neurodevelopment and adult neurotoxicity.

Methods

Sources of Information

We used the electronic data source PubMed (National Library of Medicine, Bethesda, MD, USA: http://www.ncbi.nlm.nih.gov/pubmed) to conduct two different bibliographic searches of published human studies on gene-mercury interactions for (1) toxicokinetics of mercury in child and adult populations and (2) neurological effects in child and adult populations.

Search Strategy

We selected relevant articles with an end date of 31st of August 2014. We used the following key terms or combinations of them, for the literature search:

1. Gene-mercury interactions for mercury toxicokinetics: “gene*”,“*mercury”
2. Gene-mercury interactions for neurodevelopment: “gene*”, “*mercury”, “neurodevelopment”, “cognitive”, “behaviour”, “brain”, “nervous system”, “neurotoxicity”.

Selection Criteria and Identification of Relevant Articles

Epidemiological studies of pre- and/or postnatal measures of genes and mercury interaction in association with (1) mercury toxicokinetics or/and (2) adverse effects on child neurodevelopment or/and adult neurotoxicity were selected and reviewed. The articles included these following criteria: (1) original article; (2) observational epidemiological study; (3) assessment of the exposure to IHg or MeHg in humans; (4) evaluation of neurodevelopment during childhood or/and neurotoxicity during adulthood; and (d) languages such as English, French, Spanish, Portuguese, or Italian. In addition to the search in PubMed, we searched in the references of the selected articles.

We referred to the associations or interactions as statistically significant when p values were less than 0.05. The complete name of all genes, gene families, and their potential role in mercury toxicokinetics and neurotoxicity can be found in Tables 1 and 2.

Results

Literature Review

Twenty-three articles met the inclusion criteria. Among them, 14 studied the influence of gene interactions on mercury toxicokinetics (seven on MeHg, two on IHg, and five on both), four evaluated the effect on neurodevelopment among children, and six evaluated the neurotoxicity among adults. There was one article that studied both the mercury toxicokinetics and neurotoxicity. The characteristics of the reviewed studies, including exposure levels, and main results are summarized in Tables 3 and 4. All selected studies were written in English.

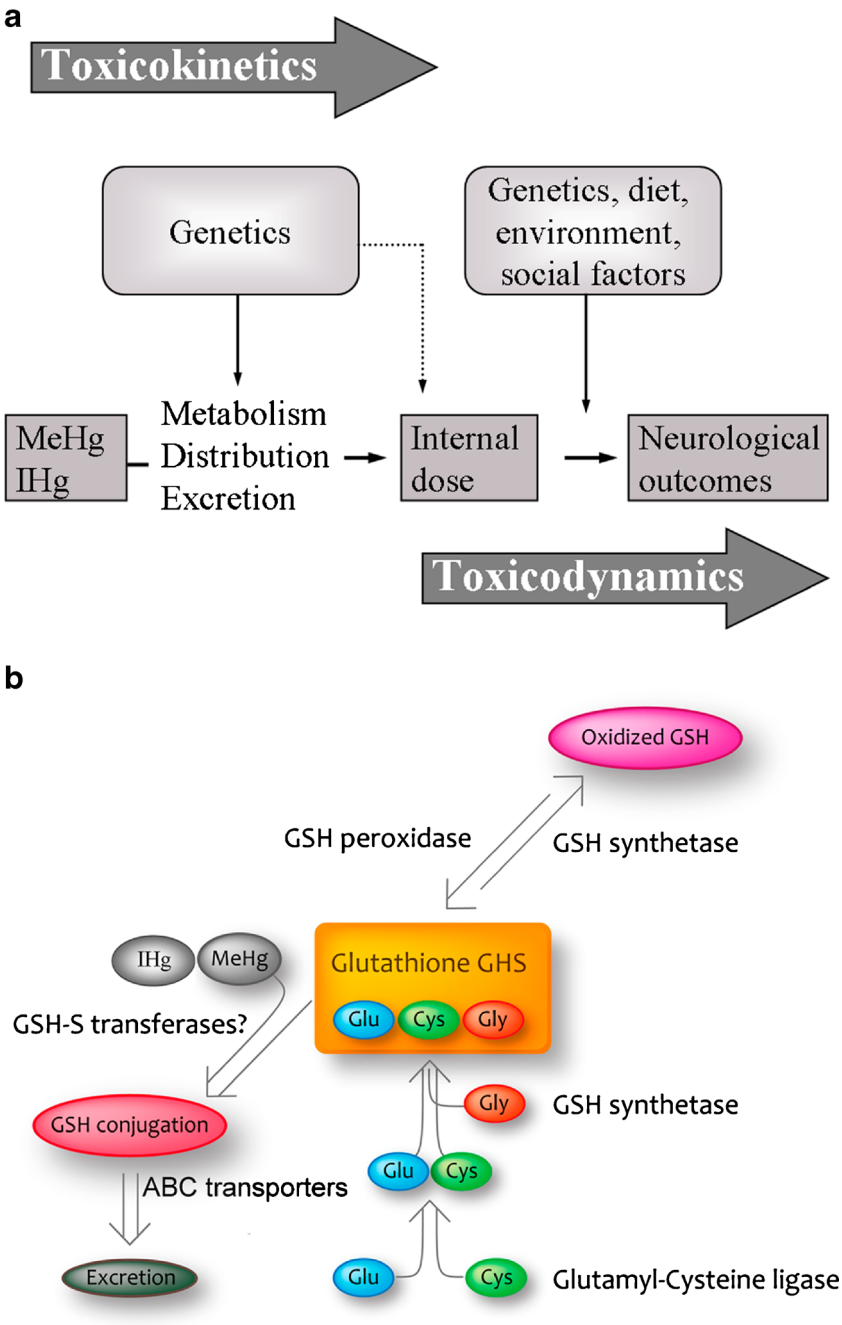

Fig. 1 **a** Scheme of how genetics can modify both mercury toxicokinetics and mercury-related neurotoxicity. **b** Mercury (IHg and MeHg) metabolism interacts with the glutathione (GSH) system pathway. Differences in mercury body burden among populations have been related to polymorphisms in genes coding for enzymes involved in glutathione (GSH) synthesis and metabolism: glutamyl-cysteine-ligase (GCL; catalytic subunit: GCLC, modifier subunit: GCLM), GSH synthetase (GS), and glutathione-S-transferase (GST), and also in genes coding for ABC transporters

Genes or Gene Families Examined in the Studies

Most articles studied the role of genes related to the small tripeptide glutathione (GSH), as the main mechanism of mercury elimination (both for inorganic and organic Hg) is through conjugation with [22] (Fig. 1b, Tables 1 and 2). Other systems of relevance for MeHg and IHg elimination and in turn toxicity were metallothionein (MTs) and genes coding for transporters (ABC, OATs, and LATs). Further, some genes with key function in the nervous system were evaluated for mercury neurotoxicity.

Genetic Effects on Mercury Toxicokinetics

Fourteen studies evaluated the effect of the genetic background on mercury concentrations in different human populations (Table 3). We grouped the manuscripts based on study population (newborn/ adults and general population/highly exposed population). Urine is the main excretion pathway for IHg [23], and total mercury concentrations (THg) in urine are common measure for exposure to IHg. Almost all MeHg ingested from fish is absorbed into the bloodstream, and in blood, 90 % of MeHg is bound to erythrocytes; the main

Table 1 Genes or gene families cited in the manuscript and their potential role in relationship with mercury toxicokinetics

Genes/family of genes		Protein function and role in Hg/MeHg toxicokinetics	Chromosome
ABC	ATP binding cassette	The superfamily of ABC transporters is a large and widely expressed protein family responsible for the active transport of various compounds across biological membranes including drugs (e.g., anticancer agents) and xenobiotics. Some of the ABC transporters transport compounds conjugate to glutathione.	–
GCLC	Glutamate-cysteine ligase, catalytic subunit	Glutamate-cysteine ligase is the first and rate-limiting enzyme of synthesis of glutathione. GCLC is the catalytic subunit of the enzyme.	6
GCLM	Glutamate-cysteine ligase, modifier subunit	Glutamate-cysteine ligase is the first rate-limiting enzyme of synthesis of glutathione. GCLM is the modifier subunit of the enzyme.	1
GST	Glutathione S-transferase	Glutathione S-transferases (GSTs) are a family of enzymes that play an important role in detoxification by catalyzing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione.	-
GSTM1	Glutathione S-transferase mu 1	The proteins encoded by these genes are members of a superfamily of proteins that catalyze the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds.	1
GSTP1	Glutathione S-transferase pi 1		11
GSTT1	Glutathione S-transferase theta 1		22
LATs	System l-amino acid transporter	Family of proteins that are involved in the transport of amino acids into cells in exchange for other amino acids.	16
MTs	Metallothioneins	Family of detoxification proteins with cysteine groups that confers mercury-binding properties and high redox capabilities	16
OATs	Organic anion transporter	Family of multispecific transport proteins located in the basolateral membrane. They mediate the uptake of a variety of substrates from renal blood.	10

Table 2 Genes or gene families cited in the manuscript and their potential role in relationship with mercury neurotoxicity

Genes/family of genes		Protein function and role in Hg/MeHg neurotoxicity	Location
5-HTT	Huntingtin (official gene name: *SLC6A4*)	Integral membrane protein that transports the neurotransmitter serotonin from synaptic spaces into presynaptic neurons.	17
APOE	Apolipoprotein E	APOE is a crucial factor involved in cholesterol metabolism, neurite growth, and neuron repair in the central nervous system.	19
BDNF	Brain-derived neurotrophic factor	BDNF is a member of the nerve growth factor family, necessary for survival of striatal neurons in the brain.	11
COMT	Catechol-O-methyltransferase	COMT that maintains neurologic functions by regulating the availability of key neurotransmitters, such as dopamine.	22
CPOX	Coproporphyrinogen oxidase	CPOX is the sixth enzyme of the heme biosynthetic pathway. The enzyme is soluble and found in the intermembrane space of mitochondria.	3
GRIN2A	Glutamate receptor, ionotropic, *N*-methyl D-aspartate 2A	GRIN2A and GRIN2B encode subunits of N-methyl-D-aspartate glutamatergic receptors, which mediate excitatory neurotransmission in the central nervous system.	16
GRIN2B	Glutamate receptor, ionotropic, *N*-methyl D-aspartate 2B		12
PON1	Paraoxonase 1	PON1 inhibits oxidation of lipoproteins through hydrolysis of lipid peroxides.	7
SEPP1	Selenoprotein P, plasma, 1	SEPP1 a selenoprotein containing multiple selenocysteine residues and has been implicated to function as an antioxidant.	5
TDO2	Tryptophan 2,3-dioxygenase	TDO2 is a heme enzyme that plays a critical role in tryptophan ans serotonine metabolism. A modification in this metabolism could lead to accumulation of serotonine in the brain and cause neurobehavioral disorders.	4
TF	Transferrin	TF transports iron from the intestine, reticuloendothelial system, and liver parenchymal cells to all proliferating cells in the body.	3

Table 3 Studies on genetic influence on mercury toxicokinetics[a]

Ref.	Location. Population (age, n)	Matrix (Hg concentrations)	Gene (polymorphism)	Results	
				Main effect	Interaction
Newborns					
[25•]	Spain, Greece, Italy. Newborns (1651)	Cord blood (GM THg: 8.2, 5.4 and 3.8 μg/L)	*ABCB1* (rs2032582)	Carriers of TT genotype had higher THg in Italy	GG higher THg with higher fish intake
			ABCC1 (rs11075290)	Carriers of C allele had higher THg in Italy and Spain	CC higher THg with higher fish intake
			ABCC2 (rs2273697)	ns	GA+AA higher THg with higher fish intake
			ABCA1 (rs3905000)	ns	ns
[28]	Korea. Pregnant women and newborns (417)	Maternal and cord blood (GM THg: 3.30 and 5.53 μg/L)	*GSTT1 (deletion)*	ns	ns
			GSTM1 (deletion)	ns	ns
Adults from the general population					
[33]	Sweden. Cases-controls of myocardial infarction (na, 1027)	Ery (AM THg controls: 4.9±5.1; cases: 4.5±5.7 μg/L)	*GCLC*-129 (rs17883901)	ns	na
			GCLM-588 (rs41303970)	Carriers of TT highest THg among controls	na
			GSTP1-105 (rs1695)	ns	na
			GSTP1-114 (rs1138272)	ns	na
[30]	Austria. Students (21 years, 324)	Blood (Mn THg: 1.34 μg/L), hair (Mn THg: 202 ng/g) and urine (Mn THg: 1.24 μg/g)	*GCLC-129* (rs17883901)	ns	na
			GSTP1-105 (rs1695)	*GSTP1*-105/*GCLC* and *GSTP1*-105/*GSTM1* combinations showed synergistic effects on hair THg compared to single-gene variants	na
			GSTP1-114 (rs1138272)	Carriers of variant allele (Val) had higher hair THg compared to carriers of AlaAla	na
			GSTT1 (deletion) *GSTM1* (deletion)	Higher hair THg in carriers of jointly homozygous deletion of *GSTT1* and *GSTM1*. Higher hair THg in carriers of homozygous deletion of *GSTT1* and *GSTP1*-114 variant genotypes.	na
			GSTA1 (rs3957356)	ns	na
			MT1A (rs11640851)	ns	na
			MT2A (rs10636)	ns	na
			MT4 (rs11643815)	Carriers of variant allele had higher THg	na
[32]	Sweden (49 years, 292)	Ery (Mn THg: 5.5 μg/L)	*GCLC-129* (rs17883901)	ns	ns
			GCLM-588 (rs41303970)	TT carriers had higher EryTHg than CT+CC	ns
			GSTP1-105 (rs1695)	Carriers of Val allele had lower Ery-THg	Positive interaction *GSTP1* IleIle+IleVal genotype and PUFAs on THg

Table 3 (continued)

Newborns

Ref.	Location. Population (age, n)	Matrix (Hg concentrations)	Gene (polymorphism)	Results	
				Main effect	Interaction
			GSTP1-114 (rs1138272)	Carriers of at least one Val allele had lower Ery-THg	Positive interaction *GSTP1* AlaAla and PUFAs on THg
[29]	Austria. Students (21 years, 192)	Blood (Mn THg: 1.51 μg/L), hair (202 ng/g), urine (1.27 μg/g)	*GSTT1* (deletion) *GSTM1* (deletion)	Carriers of homozygous deletions for *GSTM1* and *GSTT1* had significantly higher hair THg than those with other genotypes	Among fish-eaters carriers with homozygous GST deletions showed higher hair THg than GST carriers
			MT1X *MT1J*	MT expression negatively correlated with blood THg	ns
[34]	Sweden (55 years, 365)	Ery (AM MeHg: 5±5.4 μg/L)	*GCLC-129* (rs17883901)	Carriers of one variant allele (T) had higher MeHg	na
			GCLM-588 (rs41303970)	ns	na
			GSTP1-105 (rs1695)	Carriers of one variant allele (Val) had higher MeHg	na
			GSTP1-114 (rs1138272)	Carriers of Ala/Val had higher MeHg than Ala/Ala	na
			GSTA1 (rs3957356)	ns	na
			GSTM1 (deletion)	ns	na
			GSTT1 (deletion)	ns	na
Adults highly exposed to mercury					
[36•]	Indonesia, the Philippines, Tanzania, and Zimbabwe. Controls, living in gold mining population, working as gold miners (>12 years, 1017)	Urine (GM THg: Indonesia=4.2 μg/g, Philippines=2.9 μg/g, Tanzania= 1.0 μg/g and Zimbabwe=7.7 μg/g)	*ABCB1* (rs1045642)	ns	na
			ABCB1 (rs2032582)	ns	na
			ABCC1 (rs11075290)	ns	na
			ABCC1 (rs41395947)	ns	na
			ABCC2 (rs1885301)	Carriers of the A allele had higher urinary THg than those with the GG genotype	na
			ABCC2 (rs717620)	Carriers of one/ two copies of A allele had higher urinary THg	na
			ABCC2 (rs2273697)	Carriers of the A allele (Ile) had lower urinary THg than non-carriers (Zimbabwe).	na
			ABCC2 (rs3740066)	ns	na
			OAT1 (rs4149170)	Carriers of AA had lower urinary THg than carriers of AG/ GG	na
			OAT1 (rs11568626)	ns	na
			OAT3 (rs4149182)	Carriers of CC had lower urinary THg than those with CG or GG in the African population	na
			OAT3 (rs45566039)	ns	na
			SLC3A2 (rs2282477)	ns	na
			SLC3A2 (rs77030286)	ns	na
			LAT1 (rs3815559)	ns	na

Table 3 (continued)

Newborns

Ref.	Location. Population (age, n)	Matrix (Hg concentrations)	Gene (polymorphism)	Results	
				Main effect	Interaction
			LAT1 (rs33916661)	Carriers of GG showed higher urinary THg than those with GA or AA	na
			LAT2 (rs12879346)	ns	na
			LAT2 (rs12588118)		
[38]	Ecuador. Gold miners (37 years, 200), gold merchants (31 years, 37) and referents (38 years , 72)	Urine (Mn THg: 3.3, 37 and 1.6 μg/g)	*GCLM-588* (rs41303970)	Carriers of CT+TT had higher THg than CC in all groups	na
			GCLC-129 (rs17883901)	ns	na
			GSTP1-105 (rs1695)	na	na
			GSTP1-114 (rs1138272)	na	na
			GSTM1 (deletion)	na	na
			GSTT1 (deletion)	na	na
[39]	USA. Dental professionals (515)	Urine (AM THg: 1.06 μg/L) and hair (AM THg: 0.51 μg/g)	*MT1A* (rs11640851)	ns	ns
			MT1A (rs8052394)	Carriers of GA+GG had lower hair THg than AA	GA+GG lower hair THg with higher fish intake
			MT1A (rs9922957)	ns	ns
			MT1E (rs708274)	ns	ns
			MT1G (rs12315)	ns	ns
			MT1M (rs1827210)	ns	ns
			MT1M (rs9936741)	Carriers of TT had lower hair THg than TC and CC	TC higher urinary THg with higher fish intake
			MT1M (rs2270837)	Carriers of AA had lower urinary THg than GG	AA lower urinary THg with more amalgams (from personal and professional exposure)
			MT2A (rs10636)	Carriers of CC had lower urinary THg than GG	ns
			MT2A (rs28366003)	ns	ns
			MT4 (rs11643815)	ns	ns
			MTF1 (rs473279)	ns	ns
			MTF2 (rs3748682)	ns	ns
[37]	USA. Dental professional (dentists: 56 years , 244 and non dentists: 48 years , 269)	Urine (AM THg: 1.06±1.2 μg/L), hair (0.5±0.6 μg/g)	*GCLC-129* (rs17883901)	ns	ns
			GCLM-588 (rs41303970)	ns	ns
			GSTP1-105 (rs1695)	Carriers of Val lower hair THg than Ile	ns
			GSTP1-114 (rs1138272)	Carriers of Val lower hair THg than Ala	ns
			GSTT1 (deletion)	Carriers of deletion genotype associated with lower urinary THg	ns
			GSTM1 (deletion)	ns	ns

Table 3 (continued)

Newborns

Ref.	Location. Population (age, n)	Matrix (Hg concentrations)	Gene (polymorphism)	Results	
				Main effect	Interaction
			GPX4 (rs713041)	ns	ns
			GPX1 (rs1050450)	ns	ns
			GGT1 (rs5751901)	ns	ns
			GSTM3 (rs7483)	ns	ns
			GSS (rs3761144)	ns	Carriers of G higher hair THg with higher fish intake
			GSR (rs1002149)	ns	ns
			GSR (rs2911678)	ns	ns
			SEPP1 (rs3877899)	ns	ns
			SEPP1 (rs7579)	Carriers of T lower urinary THg than C	Carriers of T lower hair THg with higher fish intake
[35]	Ecuador. Gold miners (37 years, 200), gold merchants (31 years, 37) and referents (38 years , 72)	Blood (Mn THg: 5.3, 30.1 and 5.0 μg/L), urine (3.3-4.5, 36.9, 1.6 μg/g)	*GCLM-588* (rs41303970)	Carriers of T higher blood and urinary THg than C	na
			GCLC-129 (rs17883901)	ns	na
			GSTP1-105 (rs1695)	ns	na
			GSTP1-114 (rs1138272)	ns	na
			GSTM1 (deletion)	ns	na
			GSTT1 (deletion)	ns	na
			GSTA1-52	ns	na
[40•]	Brazil. Amazonian population (41 years, 88)	Whole blood (AM THg: 37±21 μg/L), plasma (THg: 10±4 μg/L and MeHg:4±3 μg/L)	*GSTP1-105* (rs1695)	ns	na
			GCLM-588 (rs41303970)	ns	na
			GCLC-129 (rs17883901)	CT+TT higher plasma THg and MeHg than CC	na
			GSTM1 (deletion)	Carriers of homozygous deletion higher plasma THg and MeHg	na
			*GSTT1 (*deletion)	ns	na
[41]	Brazil. Amazonian population (42 years, 400)	Blood (AM THg: 48.5±35.6 μg/L), hair (13.8±10.2 μg/g)	*GCLM-588* (rs41303970)	TT lower blood and hair THg than C carriers	ns
			GSTP1-105 (rs1695)	ns	ns
			GSTM1 (deletion)	Carriers of homozygous deletion higher blood and hair THg	ns
			GSTT1 (deletion)	ns	ns

[a] *AM* Arithmetic mean, *Ery* Erythrocytes, *GM* Geometric mean, *IHg* Inorganic mercury, *Mn* Median, *MeHg* Methylmercury, *THg* Total mercury concentrations, *ns* Not significant effect, *na* Not available, *Yrs*. Years

excretion routes are through bile and hair [24]. Hence, blood/erythrocytes and hair THg are common biomarkers of exposure to MeHg.

Methylmercury Toxicokinetics in Children

Two studies were conducted among newborns (Table 3). The association between maternal fish consumption in Mediterranean countries and cord blood THg was analysed in relation to the genotype of four genes encoding members of the superfamily of ABC transporters [25•]. ABC transporters are found in the blood–brain barrier, placenta, liver, gut, and kidney and they could potentially participate in the cellular export of GSH-conjugated mercury complexes in humans [26, 27] (Tables 1 and 2). Significant differences in THg were found between carriers of different genotypes of *ABCB1* and *ABCC1*, and also significant interactions were found for maternal fish intake and *ABCB1*, *ABCC1*, and *ABCC2*. For a doubling in fish intake of the mothers, children with the rs2032582 GG genotype accumulated 35 % more THg than children with TT. In a second study, the association between blood THg in Korean mothers and newborns and deletions in the glutathione S-transferases *GSTM1* and *GSTT1* were evaluated, but no significant genetic differences were found [28].

Mercury Toxicokinetics in Adults

Twelve studies evaluated the influence of different polymorphisms on mercury concentrations in adult populations (Table 3). Among them, five studies were conducted on individuals from the general population and seven on individuals highly exposed to mercury (five with occupational exposure to IHg and two where individuals with high fish consumption were selected, i.e., individuals mainly exposed to MeHg).

General Population

a. Inorganic mercury

Two studies analyzed urinary THg [29, 30] in medicine students in Austria and evaluated mercury toxicokinetics as a function of GSH- and MT-related genes. MTs are detoxification proteins that bind certain metals including mercury [31]. No significant differences in THg were found in relation to the different SNPs evaluated.

b. Methylmercury

THg was also analysed in hair and blood samples in the two studies described above on students from Austria [29, 30] and in erythrocyte samples in two studies conducted on sub-groups from the same population in northern Sweden [32, 33]. In the fifth study, speciation for MeHg was also performed in erythrocyte samples from the same Swedish population [34].

Here, THg and MeHg in blood and hair were analysed as a function of the promoter SNPs *GCLC* rs17883901 and *GCLM* rs41303970 and three of them (the three Swedish studies) observed higher THg and MeHg in erythrocytes among carriers of the variant allele (T in both genes) [32–34]. Also, two non-synonymous SNPs in *GSTP1* (rs1695 and rs1138272) were frequently studied. In Austria and Sweden [34, 30], it was found that carriers of variant alleles for both *GSTP1* variants had higher blood THg and MeHg in erythrocytes, respectively. Additionally, rs1695 showed a synergistic effect on hair THg with both *GCLC* rs17883901 and *GCLM* rs41303970, compared to individual analysis of each SNP [30]. Conversely, in a Swedish population selected for higher fish intake [32], an effect in the opposite direction was found; individuals with the variant allele Val had lower THg in erythrocytes, and the same authors [33] did not find any significant effect related to this gene.

The influences of the deletion alleles of *GSTM1* and *GSTT1* were also analyzed. Two studies from the same population in Austria [29, 30] found that individuals with homozygous deletions for both genes had higher blood THg, but in a Swedish population [34] there was no significant effect of these genotypes on THg in erythrocytes.

Populations Highly Exposed to Mercury

a. Inorganic mercury

Five studies evaluated genetic interactions on mercury toxicokinetics among individuals occupationally exposed to IHg [35, 36•, 37–39] (Table 3). Polymorphisms in transporter genes, such OATs, LATs, and ABCs, were studied in relation to urinary THg in gold miners and controls from Africa and Asia [36•]. Significant associations were found as a function of *ABCC2*, *OAT3*, and *LAT1* genotypes. Urinary THg were higher among *ABCC2* rs1885301 and rs717620 A-allele carriers and *ABCC2* rs2273697 G-allele carriers. The *LAT1* rs33916661 GG genotype was associated with higher THg in all populations, and *OAT1* rs4149170 and *OAT3* rs4149182 were associated with THg mainly in the Tanzanian study groups. Urinary THg as a function of *GCLC*, *GCLM* and GST's polymorphisms were evaluated in gold miners in Ecuador [38]. Here, *GCLM* rs41303970 T-allele carriers had statistically significant higher THg, but authors did not find significant differences as a function of *GCLC* rs17883901, *GSTA1*-52, *GSTM1* or *GSTT1* deletions, *GSTP1* rs1695, or *GSTP1* rs1138272 genotypes. In Ecuadorian gold miners, the presence of T allele in *GCLM* rs41303970 was related to increased blood THg [35].

Two studies evaluated the influence of polymorphisms in MTs, *GCLM*, *GCLC*, GSTs, and *SEPP1* on urinary

Table 4 Studies on the effect of gene-mercury interactions on child neuropsychological development and adult neurotoxicity[a]

Ref	Location. Population (age, n)	Matrix. Hg concentrations	Neurodevelopmental test and domain	Genes	Polymorphism	Association between Hg and neurodevelopment	Hg*G p-value
Children							
[44]	Taiwan. Children (2 years, 168)	Cord blood AM THg 14.7±8.7 μg/L	CBCL. Total problems, Internalizing, Externalizing, Emotionally reactive, Anxious/depressed, Somatic complaints, Withdrawn, Attention problems, Aggressive behavior, Sleep problems	*APOE*	3 alleles: ε2, ε3, ε4	+ (impaired behaviour) among ε4 allele carriers and THg >12 μg/L	na
[45]	Portugal. Children (8–12 years, 330)	Urine. AM THg Boys 2 and 7 years: 2.17 (2.02) and 1.25 (3)μg/g. AM THg girls 2 years and 7 years: 2.86(2.63) and 1.77(2.27) μg/g	Children were evaluated at 2 and 7 yrs. RAVALT, subtests from the WRAVMA, WISC-III, WMS-III, SRT, FT, TA and TB, SWT, and WCS. Attention/Concentration, Visual-Spatial, Learning & Memory, Motor	*CPOX*	rs1729995	Attention, motor (2 years) and all domains (7 years): − among boys with variant allele	≤0.05
				CPOX	rs1131857	Learning & Memory (2 years) - among girls with variant allele	
						Executive function (7 years): + (impaired performance) among girls with variant allele	
				MT1M	rs2270837	Learning & memory, motor (2 years) and learning & memory (7 years): − among boys with variant allele	≤0.05
						Learning & memory (7 years): − among girls with variant allele	
				MT2A	rs10636	Attention (2 years) and visual-spatial, learning & memory (7 years): − among boys with variant allele	≤0.05
				TDO2	rs3755907	Motor (2 years) and attention, visual-spatial, motor (7 years): −among boys with variant allele	≤0.05
						Learning & memory, executive learning (7 years): + (improved performance) among girls with variant allele	
				COMT	rs4680	Attention, learning & memory (2 years) and attention, visual-spatial (7 years): − among boys with variant allele	≤0.05
						Attention, executive function (2 years): + (impaired performance) among girls with variant allele	
						Learning & memory (7 years): − among girls with variant allele	
				COMT	rs4633	Attention, learning & memory (2 years) and attention, visual-spatial (7 years): − among boys with variant allele	≤0.05
						Attention, executive function (2 years): + (impaired performance) among girls with variant allele	
				COMT	rs4818	Attention (2 years): + (improved performance) among girls with variant allele	≤0.05
				COMT	rs6269	Attention, learning & memory (2 years) and visual-spatial	≤0.05

Table 4 (continued)

Ref	Location. Population (age, n)	Matrix. Hg concentrations	Neurodevelopmental test and domain	Genes	Polymorphism	Association between Hg and neurodevelopment	Hg*G p-value
						(7 years): − among boys with variant allele Learning & Memory (2 years): + (improved performance) among girls with variant allele	
				GRIN2A	rs727605	Attention, learning & memory (2 years) and attention (7 years): − among boys with variant allele	≤0.05
				GRIN2B	rs7301328	Learning & memory, motor (2 years and 7 years): − among boys with variant allele Learning & memory (2 years and 7 years): − among girl with variant allele Motor (2 years): + (improved performance) among girls with variant allele	≤0.05
				BDNF	rs6265	Learning & memory (2 years): − among boys with variant allele Learning & memory (2 years and 7 years): − among girls with variant allele	≤0.05
				GSTT1	deletion	Motor (2 years) and attention, learning & memory (7 years): − among boys with variant allele Attention (2 years): + (impaired performance) among girls with variant allele Motor (2 years): − among girls with variant allele	≤0.05
				SLC6A4	insertion/ deletion	Attention, learning & memory (7 years): − among boys with variant allele	≤0.05
				KIBRA	rs17070145	Attention, visual-spatial, learning & memory (7 years): − among boys with variant allele	≤0.05
				APOE	rs429358, rs7412	Learning & memory (7 years): − among boys with ε4 allele Attention, motor (7 years): + (improved performance) among girls with ε4 allele	≤0.05
[42•]	UK. Children (8 years, 1311)	Cord tissue. AM THg 26±13 ng/g	WISC III. Total, verbal and performance IQ	*TF*	rs3811647	Performance scores: − among AA carriers.	0.08
				PON1	rs662	Total IQ: + among TT carriers.	0.02
				BDNF	rs2049046	Performance scores: − among AA carriers	0.07
[43]	Taiwan. Children (2 years, 168)	Cord blood. 52.3 % with THg levels >12 μg/L	CDIIT. Whole test, cognitive, language, gross-motor, fine-motor, motor, social, and self-help	*APOE*	3 allels (ε2, ε3, ε4)	Whole test: − among ε4 allele carriers Cognition: − among ε2 and ε4 alleles carriers Social: − among ε4 allele carriers	≤0.05
Adults							
[38]	Ecuador. Gold miners (37 years, 200), gold merchants (31 years, 37) and referents (38 years, 72)	Urine. Mn THg: 3.3, 37 and 1.6 μg/g	NtS. Postural tremor, hand coordination, reaction time, postural stability	*GCLM*	rs41303970	ns	na
				GCLC	rs17883901	ns	na
				GSTA1		ns	na
				GSTM1	deletion	ns	na
				GSTT1	deletion	ns	na
				GSTP1	rs1695	ns	na

Table 4 (continued)

Ref	Location. Population (age, n)	Matrix. Hg concentrations	Neurodevelopmental test and domain	Genes	Polymorphism	Association between Hg and neurodevelopment	Hg*G p-value
				GSTP1	rs1138272	ns	na
[48]	USA. Male dentists (49 years, 183) and female dental assistants (36 years, 213)	Urine. AM: 2.4 (2.1) and 1.8 (1.8) μg/dL	BEES, WMS, MDT, POMS: Attention, working memory, sustained attention, visual memory, perception, visuomotor speed, cognitive flexibility, reaction time, response speed and tracking, different mood states	*SLC6A4*	insertion/ deletion	Cognitive flexibility, manual coordination, and some mood states: − among dentists with variant allele	na
						Attention, working memory, manual coordination, and some mood states among dental assistants with variant allele	na
[50]				*COMT*	rs4680	Some mood states: among dental assistants *COMT* variant allele	na
[47]				*CPOX4*	rs1131857	Visuomotor: − among dental assistants and dentists with CPOX4 variant allele	na
[46]				*BDNF*	rs6265	Among variant allele carrier: coordination: − among dentists and dental assistants. Cognitive flexibility: − among dental assistants.	na
[49]						Increased symptom and mood scores among variant allele carriers	na

\+ Direct association

\- Inverse association

[a] *AM* Arithmetic mean, *BEES* Behavioural evaluation for epidemiologic studies, *CDIIT* The Comprehensive developmental inventory for infants and toddlers, *CBCL* Child behaviour checklist, *CT* Colour and word–colour tests, *FT* Finger tapping test, *na* Not available, *NtS* Neurobehavioral test system, *MDT* Manual dexterity test, *POMS* Profile of mood states, *RAVALT* Rays verbal learning test, *RAVLT* Rey auditory verbal learning test, *Ref.* References, *SRT* Simple reaction time, *SWT* Stroop word test, *TA and TB* Trailmaking A and B, *THg* Total mercury concentrations, *WAIS-III* Wechsler adult intelligence scale-III, *WCS* Wisconsin card sort, *WISC III* Wechsler intelligence scale for children III, *WMS-III* Wechsler memory scale for adults-III, *WRAVMA* Wide range assessment of memory and learning and visual motor abilities

THg among American dental professionals [37, 39]. Subjects with the *MT1M* rs2270837 AA genotype or the *MT2A* rs10636 CC genotype had lower urinary THg than did those with the *MT1M* or *MT2A* GG genotypes. Further, in the same study population [37], it was found that the deletion genotype of *GSTT1* and the allele T of *SEPP1* rs7579 were associated with lower urinary THg.

b. Methylmercury

Two studies conducted in a high fish-eating population from the Brazilian Amazonas showed that subjects with homozygous deletion of *GSTM1* had higher blood and hair THg than subjects with the *GSTM1* genotype, and further, that individuals with *GCLM* rs41303970 TT genotype had lower THg [40•, 41].

The influence of some GSH- and MTs-related genes was studied in relation to THg in hair of dental professionals [37, 39]. Subjects with *MT1A* rs8052394 GA and GG genotypes or the *MT1M* rs9936741 TT genotype had lower hair THg than did subjects with *MT1A* AA or *MT1M* TC and CC genotypes, respectively [39]. Furthermore, it was found that Val-alleles of *GSTP1* rs1695 and rs1138272 were associated with decreased hair THg [37].

Effect of Gene-Mercury Interactions on Neurodevelopment and Neurotoxicity

Effect of Gene-Mercury Interactions on Neurodevelopment in Children

Four studies evaluated the effect of gene-mercury interactions on neurodevelopment among populations <18 years (Table 4).

Three of them were birth cohort studies and evaluated prenatal exposure to MeHg by THg in cord blood/tissue samples [42•, 43, 44]. Two of these studies [43, 44] were conducted on the same population in Taiwan and evaluated the interaction between THg in cord blood and the *APOE* gene on neurodevelopment in 2-year-old children. The authors found that children carrying the ε4 allele showed impaired scores for the whole test, as well as for parts related to cognition, and social domain, the interaction between *APOE* and THg concentrations was significant for these neurodevelopmental domains [43]. In a further study, mercury-related impairment in different behavioral domains (total problems, internalizing, externalizing, emotionally reactive, anxious/depressed, and aggressive behavior) was observed only among children carrying the ε4 allele [44].

Another birth cohort study (ALSPAC cohort) from UK evaluated the interaction between prenatal exposure to THg in cord tissue and 247 SNPs within 66 genes in 8-year-old children [42•]. Children with AA genotype of *TF* rs3811647 or *BDNF* rs2049046 showed negative and statistically significant associations between THg and performance scores. The *p* values for the interaction genotype*THg were marginally significant for both genes. Children with *PON1* rs662 TT genotype showed a positive and statistically significant association between THg and total IQ scores.

Children in the Casa Pia Children's Amalgam Clinical Trial study in Portugal were genotyped for 27 SNPs in 13 genes, and postnatal exposure to IHg was measured as THg in urine samples taken annually from the children between 2 and 7 years of age [45]. The relationship between THg and neurodevelopmental domains as a function of different genotypes was evaluated in 2- and 7-year-old boys and girls. Several statistically significant gene-mercury interactions were found on different domains. Boys' variant alleles carriers for *CPOX* rs1729995, *MTM* rs2270837, *MT2A* rs10636, *TDO2* rs3755907, *COMT* rs4680, *COMT* rs4633, *COMT* rs6269, *GRIN2A* rs727605, *GRIN2B* rs7301328, *BDNF* rs6265, *GSTT1* deletion polymorphism, *SLC6A4* insertion/deletion, *KIBRA* rs17070145, or *APOE* ε4 obtained mercury-related impaired scores in different neurodevelopmental domains. The associations between THg and the tests scores were positive in girls' variant allele carriers for *TDO2* rs3755907, *COMT* rs4818, *COMT* rs6269, *GRIN2B* rs7301328, and *APOE* ε4. For more details see Table 4.

Effect of Gene-Mercury Interactions on Neurotoxicity in Adults

Six studies evaluated gene-mercury interactions for neurotoxicity in adults with occupational exposure to IHg. In gold miners from Ecuador, the interaction of urinary THg with GST-related genes was evaluated in relation to tremor and performance in coordination tests but no significant associations were found [38]. The other five studies were conducted on the same population of American dental professionals, and the interaction of urinary THg with *SLC6A4*, *COMT*, *CPOX4*, and *BDNF* was evaluated with several neurological outcomes [46–50, 15]. Some significant additive interactions were observed; carriers of *SLC6A4* variant allele showed a negative effect on cognitive flexibility, manual coordination, attention, working memory, manual coordination, and some mood states [48]. Some mood states were also associated with IHg and *COMT* rs4680 [50], and detrimental effects on visuomotor domain were observed among *CPOX4* rs1131857 variant allele carriers [47]. The variant allele in *BDNF* rs6265 was associated with impaired coordination and some mood states [46, 49].

Discussion

The amount of literature about genetic influences on mercury (both IHg and MeHg) toxicokinetics is still limited and focused mainly on adult populations (general, occupationally exposed, or high fish consumers). Fetuses and children are the population sub-groups that are more vulnerable to the neurotoxic effects of MeHg, and the bibliography on them is really sparse.

Due to the central role of the GSH molecule in mercury metabolism, the GSH-related genes were the most frequently studied, both for Mehg and IHg, but the results were, apart from one gene (*GCLM*), contradictory, the same alleles were associated to higher and lower mercury concentrations in different populations. Information regarding the effect of gene-mercury interactions on neurodevelopment and neurotoxicity is too scarce to draw a definite conclusion, but one gene (*APOE*) with consistent results in different studies on children was identified. Neurotoxicity associated with IHg-gene interactions in adults has been assessed in few cross-sectional studies on occupationally exposed populations, and *BDNF* might be a candidate gene to follow-up on in future studies.

If we address the studies in more detail, *GCLM* rs41303970 seems so far to be the most promising genetic polymorphism for mercury toxicokinetics among the GSH-related genes studied. In two studies, the T allele for *GCLM* rs41303970 was associated with higher erythrocytes THg in general population from Sweden [32, 33], and higher urinary THg in gold miners from Ecuador [35, 38]. However, individuals from a high fishing eating population from Brazil with TT genotype had lower hair and plasma THg concentrations [40•]. For the other GSH-related genes, the results are more conflicting. The variant alleles of *GSTP1* rs1695 and rs1138272 were associated with higher THg and MeHg in general populations from Austria [30] and Sweden [34], and with lower THg in Sweden [32] and dental professionals from USA [37]. The T allele of *GCLC* rs17883901 was associated with increased THg in Sweden [34] and Brazil [41], and the *GSTM1* deletion genotype was associated with increased THg in general population from Austria [29, 30] and Brazil [40•, 41]. However, the number of studies without a statistically significant association is sizeable for both *GCLC* and *GSTM1* genes (n=6 and 5, respectively). GSH system is developed for protection against many different endogenous and xenobiotic substances, and polymorphisms resulting in less efficient proteins are probably compensated by other proteins in the same pathway.

The systems coding for MTs and transporter proteins in relationship to mercury concentrations have been less frequently studied, but some significant results were observed. Wang et al. (2012) studied mercury concentrations as a function of some MTs polymorphisms among dental professionals [39], and they found some statistical significant associations regarding the *MTI* and *MT2* isoforms in relation to hair and

urinary THg. Significant differences in THg as a function of *MT4* rs11643815 have been observed in students from Austria [30]. Among potential mercury-transporting proteins, *ABCB1* rs2032582, *ABCC1* rs11075290, and *ABCC2* rs2273697 were associated with THg accumulation in the fetus from maternal fish intake [25•], and *ABCC2* rs1885301, rs717620, and rs2273697 were related to IHg metabolism in a gold mining population [36•]. Considering that these studies were performed on rather large populations, *ABCC2* rs2273697 could be a candidate SNP to follow in other populations exposed to MeHg or IHg. Moreover, the evidence for an important role of ABCC1 in MeHg accumulation and neurotoxicity in fruit flies suggests that this is a transporter to be further studied in relation to MeHg exposure [51].

On the basis of available literature, we can postulate several reasons for the discrepancy between studies. First, differences could depend on the compound of mercury analyzed (IHg or MeHg), the matrix where mercury was analyzed (blood, hair, or urine is related to different kinetics of mercury in the human body) and mercury concentrations (different genetic response depending on dose). Secondly, sample size is an important factor that must be considered carefully in the assessment of interactions. Thirdly, the xenobiotic defence (GSH related, MTs, and transporters) encoding genes are highly polymorphic and other functional SNPs in linkage disequilibrium with the SNPs and with different allele frequencies in different populations analysed might explain some inconsistencies between studies. Still, there were very few attempts to consider the effects of haplotypes of gene-gene interactions in the studies evaluated, mainly due to low power of the studies. Fourthly, publication bias may be another factor since studies with statistically significant findings are more likely to be published than are studies with null results.

In the few studies on the effect of gene-mercury interaction on neurodevelopment, one polymorphism in *APOE* appeared to modify the mercury toxicity. *APOE* gene plays an important role in lipid-transported proteins and it is known to be a crucial mediating factor in neuronal repair. Three APOE alleles have been identified: ε2 has two cysteine amino-acids in its structure, ε3 has one cysteine and one arginine, and ε4 has two arginine amino-acids and no cysteine. Cysteine, with its sulfhydryl (−SH) bonds, is potentially able to bind to, and remove metals from nervous tissues, whereas arginine, lacking the -SH bonds, would be unable to do this and more toxicity might be expected [52]. Two studies conducted on the same study population from Taiwan found that children who were allele ε4 carriers obtained the worst scores in neuropsychological tests [43, 44]. Another study conducted in Portugal observed a statistically significant interaction between urinary THg, *APOE*, and sex; boys' carriers of *APOE* allele ε4 obtained impaired scores in learning and memory and girls obtained improved scores in attention and motor domains [45]. In fact, these authors found other statistically significant gene-mercury-sex interactions, which, overall, were negative among boys and positive among girls. This fact suggests a sexual different role in the influence of gene-mercury interactions on neuropsychological development, but this should be confirmed in further studies.

Another interesting gene for future studies is *BDNF*. BDNF is a protein that regulates neuronal growth and differentiation in the nervous system. A polymorphism in *BDNF* gene (rs6265) which substitutes methionine (Met) to valine (Val) at amino acid position 66 has been identified and associated with the processing and secretion of BDNF protein, Met carriers had reduced hippocampal activity in comparison with Val homozygotes [53]. Statistically significant interactions were observed regarding polymorphisms in *BDNF* in both children in the UK [42•] and in Portugal [45]. THg was associated with impaired performance scores among *BDNF* rs2049046 AA genotype carriers and also with impaired learning and memory domains in the Portugese children with the variant allele for *BDNF* rs6265. Further, *BDNF* rs6265 Met allele was found to have a role in the vulnerability to neurological damage among dental professionals exposed to IHg [46, 49].

Regarding gene-mercury interactions on child neurodevelopment and on adult neurotoxicity, there are some limitations that should be taken into account. First, there could be heterogeneity in the evaluation of the phenotypes. Children are evaluated at different ages when vast psychological changes occur and using a great variability of neuropsychological tests, which make the comparison between studies difficult and the performance of a meta-analysis unfeasible. Also, the number of polymorphisms evaluated in some of the studies is sizeable, thus the probability of spurious associations is high. Other limitations, previously commented for studies on mercury toxicokinetics, are the limited sample size and publication bias.

Conclusions

The number of studies about the genetics influence on mercury toxicokinetics is still limited and most of them were focused mainly on adult populations. Moreover, there are very scarce evidences for the effect of gene-mercury interactions on child neuropsychological development and adult neurotoxicity to draw any definite conclusion and further studies are highly warranted. Differences in the study population (age for neurodevelopment testing), mercury exposure assessment (concentrations, biological matrices, timing of exposure, and compounds of mercury), small sample sizes, and the neuropsychological tests used for the evaluation make the comparison between studies difficult and could be the cause of the contradictory results observed. More investigations about this topic are required. Additionally, environmental epidemiologic

studies should be properly designed to study the effect of genetic interactions without bias. Birth cohort studies with a prospective follow-up of children and detailed information about socio-demographic characteristics, exposure assessment, and neurodevelopment are encouraged.

The review identified a few candidate genes in the literature that could be important for genetic susceptibility to mercury. However, so far, the candidate gene approaches have not identified any major gene/s strongly modifying the kinetics or neurotoxicity of mercury, suggesting that these might be polygenic traits or that the major gene/s have not yet been identified. The explorative genome-wide analysis could be a suitable method in order to identify genetic variants important for mercury kinetics and neurotoxicity.

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Compliance with Ethics Guidelines

Conflict of Interest Sabrina Llop, Ferran Ballester, and Karin Broberg declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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