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Genetic polymorphisms are associated with exposure biomarkers for metals and persistent organic pollutants among Inuit from the Inuvialuit Settlement Region, Canada

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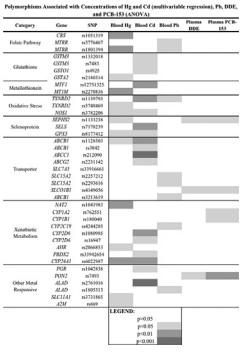
HIGHLIGHTS

- Inuit populations are exposed to high levels of environmental contaminants.
- Genetic susceptibility of Inuit populations to contaminant accumulation is unknown.
- We identified several polymorphic genes associated with contaminant levels.
- Genotypes may influence exposure-biomarker relationships

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Inuit are exposed to some of the highest levels of contaminants worldwide. Studies suggest that several genes that mediate the metabolism of these contaminants are polymorphic. We hypothesize that single nucleotide polymorphisms (SNPs) in such genes may underline differences in biomarker concentrations and/or modify exposure-biomarker associations.
Methods: Members from the Inuvialuit Settlement Region (Canada) were recruited. Blood concentrations of mercury (Hg), cadmium (Cd), lead (Pb), dichlorodiphenyldichloroethylene (DDE), and polychlorinated biphenyl (PCB-153) were measured. SNPs from pathways such as glutathione, metallothionein, oxidative stress, and xenobiotic transport were genotyped in 281 participants, and data from 112 SNPs were included in the analyses. Surveys were administered to obtain information on demographics, and key sources of Hg (diet) and Cd (smoking) exposure. ANOVA and linear regressions were used for data analyses.
Results: Geometric mean concentrations of metals were 4.6 μg/L for Hg, 1.3 μg/L for Cd, and 32.2 μg/L for Pb. Concentrations of organic pollutants were 2.0 μg/L for DDE and 0.6 μg/L for PCB-153. Biomarker levels for Hg, Cd, Pb, DDE, and PCB-153 differed ($p < 0.05$) by genotype for 4, 3, 4, 3, and 3 SNPs, respectively. In multivariable analyses

Abbreviations: Cd, Cadmium; DDE, Dichlorodiphenyldichloroethylene; Pb, Lead; Hg, Mercury; ISR, Inuvialuit Settlement Region; MAF, Minor allele frequency; PCB, Polychlorinated biphenyl; SNP, Single nucleotide polymorphism.

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Single nucleotide polymorphism
Pollutant

(for Pb, DDE, PCB-153) adjusting age, sex and body mass index (BMI), only 2 associations (one for Pb and one for DDE) remained significant. In multivariable analyses accounting for sources of Hg or Cd exposure, 24 SNPs (9 for Hg, 15 for Cd with 4 overlapping) had significant ($p < 0.05$) main effects on biomarker levels and/or modified exposure-biomarker associations.

Conclusion: The findings suggest that polymorphisms in key environmentally responsive genes can influence biomarker levels and/or modify exposure-biomarker associations for contaminants of concern to Arctic populations. Consideration of such gene-environment results may help improve the ability to conduct exposure (and ultimately risk) assessments of country foods and Inuit health.

1. Introduction

Contamination of the Arctic ecosystem and its Peoples remains of great societal concern (AMAP, 2015). Certain contaminants, such as methylmercury, dichlorodiphenyldichloroethylene (DDE), and polychlorinated biphenyls (PCBs), undergo long-range atmospheric transport and eventually bioaccumulate and biomagnify in the Arctic food chain, whereas other chemicals are sourced locally as by-products of smoking (e.g., cadmium (Cd)) or hunting (e.g., lead (Pb) in shots). Biomonitoring studies have revealed that local Inuit communities are exposed to relatively high doses of these chemicals (Laird et al., 2013a; Laird et al., 2013b). For example, focusing on women of child bearing age who participated in the 2007–2008 Inuit Health Survey, 31% had blood mercury (Hg) levels that exceeded Health Canada's guidance value, and 10% had blood Pb levels that exceeded the U.S. Centers for Disease Control's blood reference value (AMAP, 2015).

Relating biomonitoring data (i.e., blood concentrations) to health guideline values is a critical feature of decision-making and risk assessment. However, guideline values are derived to protect the entire population and thus may over- or under-protect particular segments of the population and thus lead to erroneous decisions. Risk assessments attempt to account for such variability by utilizing default uncertainty factors (Basu et al., 2014). Uncertainty factors increase the margin of safety in an effort to protect sensitive subgroups, but in doing so they may still prove to be insufficient or perhaps even over-protective. As we embark upon next-generation risk assessment (Zeise et al., 2013), there is a need to harness ecogenetic approaches (e.g., incorporating genetic polymorphisms) to help increase understanding of true biological variation across and within individuals and ethnic groups so that uncertainty factors are refined and risk assessments improved (Basu et al., 2014). This is especially necessary for Inuit populations in which there remain profound public health challenges associated with balancing the risks (i.e., contaminants) and benefits (e.g., nutritional value, cultural linkages, recreation opportunities) of consuming country foods (Donaldson et al., 2010; Kuhnlein et al., 1991; Laird et al., 2013a). While there is a relatively large evidence base concerning contaminants in country foods, there is limited information on potential genetic susceptibilities in these communities and judgments are made in relation to guidelines established for general (i.e., non-Inuit) populations (e.g., Health Canada guidelines or provisional Tolerable Daily Intake values, or U.S. EPA's Reference Doses). As stated in the 2009 AMAP Human Health Assessment, "too little is known about the genetics of [Arctic] populations to elucidate the implications of contaminant-genetic interactions on health. Because the genetic background of the Inuit differs compared with Caucasians these genetic differences must … become a part of the future studies on Arctic populations because the genotype may be fundamental to the effects of exposure to environmental contaminants".

Little information is available on gene-contaminant interactions in Inuit populations. Ghisari et al. (2013) studied 3 single nucleotide polymorphisms (rs1048943 in cytochrome P450 *CYP1A1*, rs1056836 in *CYP1B1*, and rs4680 in catechol-*O*-methyltransferase) in relation to serum levels of PCB-153 and DDE in 254 Greenlandic Inuit, and found significant differences in contaminant levels according to genotype. They also documented that the genotype and allelic frequencies of these 3 SNPs differed significantly between Inuit and Europeans thus establishing a need to expand this type of research. The objectives of this study were to determine 351 single nucleotide polymorphism (SNP) genotypes from blood samples obtained from the participants of the Inuit Health Survey (2007–2008) from the Inuvialuit Settlement Region (ISR) (Saudny et al., 2012), and to relate these genetic data to the dietary exposure estimates and blood concentrations of Hg, Cd, Pb, DDE, and PCB-153 (Laird et al., 2013a) in order to assess whether polymorphisms in key environmentally responsive genes can influence blood contaminant biomarker levels and/or modify exposure-biomarker associations for contaminants. The ultimate goal of this work is to better characterize environmentally-responsive genes and gene-environment interactions within an Inuit population in order to improve risk assessment and decision making.

2. Methods

2.1. Study sample

During the Inuit Health Survey (August to September 2007, and August to October 2008), 288 households were randomly selected for participation from the ISR in Canada as described in detail elsewhere (Saudny et al., 2012). All non-pregnant individuals 18 years of age or older were informed about the study objectives and procedures, and 362 were enrolled. Of these 362 individuals, blood samples were obtained from 288. From these blood samples, 285 samples were technically acceptable for genotyping and 281 samples were successfully genotyped. Contaminant measurements were available from 249 participants (for metals) and 248 participants (DDE, PCB-153). While 234 participants had complete datasets, participants with the appropriate data for a given analysis (e.g., Hg and SNPs) were included. Institutional Review Board approval was obtained from the Faculty of Medicine (McGill University), and necessary approvals obtained from the ISR health authority.

2.2. Blood and biomarkers

Blood was collected from the median antecubital vein by trained phlebotomists into 10 mL plastic vacutainers coated with K2-EDTA as previously described (Laird et al., 2013a). Total metal (Hg, Cd, Pb) concentrations in whole blood samples and plasma DDE and PCB-153 were quantified as described previously and reported as μg/L (Laird et al., 2013a).

2.3. SNP selection and genotyping

Genomic DNA was isolated from 2 mL of each participant's whole blood (Puregene, Gentra System, Minneapolis, MN) according to the manufacturer's protocol, was quantified using the Nanodrop 2000 spectrophotometer (Thermo Scientific, Wilmington, DE), and diluted in Tris-EDTA to 100 ng/μL. Three hundred sixty SNPs were selected a priori that were hypothesized to underlie inter-individual differences in the