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Genomics of Detoxification: How Genomics can be Used for Targeting Potential Intervention and Prevention Strategies Including Nutrition for Environmentally Acquired Illness

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ABSTRACT

Due to their genomic variants, some individuals are more highly affected by toxicants than others. Toxicant metabolizing and activating variants have been linked with a wide variety of health issues including an increased risk of miscarriages, birth defects, Alzheimer's, benzene toxicity, mercury toxicity and cancer. The study of genomics allows a clinician to identify pathways that are less effective and then gives the clinician the opportunity to counsel their patients about diet, supplements and lifestyle modifications that can improve the function of these pathways or compensate to some extent for their deficits. This article will review a few of these critical pathways relating to phase I and phase 2 detox such as GSTP1, GPX1, GSTT1 deletions, PON1 and some of the CYP 450 system as examples of how an individual's genomic vulnerabilities to toxicants can be addressed by upregulating or downregulating specific pathways via genomically targeted use of foods, supplements and lifestyle changes.

KEYWORDS

Genomics; environmental illness; GSTP1; GPX1; GSTT1 deletion; toxicants; glutathione

Introduction

When discussing toxicants, many people think of pollution and chemicals that are released into the world's water and air. Toxicants, however, are any substances that are not beneficial and are thus "toxic" to human tissue. These certainly include benzene, and various polyaromatic hydrocarbons from gasoline, coal and biofuels and other particulates found in air pollution. It also includes toxicants such as mercury and other heavy metals and pesticides. People are exposed to these elements when they breathe polluted air, eat contaminated foods, drink contaminated water, as well as from dental and other occupational and even leisure exposures.

Toxicants are innately dangerous. However, some people are more highly affected by toxicants due to variants in their inherited, genetically coded detoxification pathways. The study of genomics allows a clinician to identify pathways that are less effective and then gives the clinician the opportunity to counsel their patients about diet, supplements and lifestyle modifications that can improve the function of these pathways or compensate to some extent for their deficits. A review a few of these critical pathways will demonstrate the importance and understanding of how an individual's genomically programed detox pathways can affect their health and well-being. This review will then show how nutritionists, physicians and other clinicians can use this information for developing plans for personalized, genomically targeted, prevention and intervention strategies.

Background

Brief review of genomics

Genomics, the study of variants and the genetic code, is at the forefront of personalized medicine. Genomics is a powerful tool for physicians, nutritionists and other clinicians due to its ability to explain some of the differences people have in response to environmental exposures to toxicants, their predisposition to various diseases and health risks such as Alzheimer's, cataracts, obesity, cancer and a multitude of other chronic illnesses, as well as their requirements for various nutrients.

As a short review, DNA, the molecular premise of complex genetic codes, functions by getting transcribed into RNA, which in turn gets translated into proteins, enzymes and nutrient carriers, which are amongst the primary functional units of our bodies. The sequence of amino acids, whose size and charge define a protein's shape and ultimately their role in biological pathways, is directly chosen by every three letters of RNA, or "codon" (1). DNA also can self-regulate transcription rates based on sequences outside of the regions directly coding for proteins (2). These introns and other non-translated areas of DNA used to be referred to as "junk DNA", but scientists have shown these areas to contain crucial regulatory sequences.

Variants in DNA can have dramatic effects on an individual. When one "letter" of our DNA is changed, deleted, or added in, it can change the amount of transcribed RNA or the code for the resultant protein. These variants or

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"polymorphisms" can be found across all genes and chromosomes, affecting their proteinaceous products, and thus the efficacy of our systems that rely upon them. People want their pathways to be functioning properly of course, but for some individuals their biological difficulties are prewritten at conception when ancestral variants, acquired over millennia of small accidental changes, are passed onto them. This brings us back to the high susceptibility some face for toxicant-related illnesses.

Role of reactive oxygen species

Returning to toxicants, it is beneficial to look at one of the common endpoints of toxic damage to systems, Reactive Oxygen Species (ROS). Though this is not the only toxic endpoint this article will go into, it is certainly one of the most important. ROS, as the name implies, are molecules in the body that contain oxygen and are highly reactive. These ROS often function as oxidative agents, taking electrons from biological molecules such as lipids, DNA, and proteins. Created most prominently as natural byproducts of mitochondrial function, at healthy levels ROS serve in cell signaling to activate and deactivate various cellular pathways (3) and are functional parts of our immune system, utilized to harm pathogen invaders (4). Oxidation can also have a variety of deleterious effects, including the induction of mutation in DNA, denaturation of proteins resulting in a loss of function, or disruption of lipids and membranes that section off and protect cells (5). Thus, pathological increases in ROS levels contribute to a negative state described as oxidative stress. This can occur either due to increased generation or decreased clearance of reactive species—the latter, especially, is where genetic variants come into play.

Discussion of subject

Glutathione as the master detox pathway

Shifting focus back to the genomics of eliminating toxicants, glutathione and its related pathways are an appropriate place to start. The "master" detox pathways for both removing toxicants from the body via conjugation and for reducing and eliminating oxidative stress and free radicals are both heavily dependent on glutathione. Thus, many of the individuals more susceptible to various types of environmentally triggered illnesses, including general adverse reactions with high exposure to toxicants (6), increased risk of renal disease (7), cataracts (8), lung cancer (9, 10), and neurodegenerative issues such as MS (10) and Parkinson's (11) have problems with some of the most significant glutathione pathways.

The seriousness of impaired glutathione pathways can be seen when toxin levels are taken to extremes. In 2011, Dr. Paz-y-Mino, an epidemiologist and geneticist in Ecuador, conducted a number of studies where he looked at communities exposed to very high levels of glyphosates (Roundup™, etc.) due to aerial spraying in these coffee growing communities. What he found was that women who had variants on both chromosomes of either the crucial glutathione conjugation pathway (GSTP1 Ile105Val) or the main glutathione enzyme responsible for removal of ROS and attenuation of oxidative stress (GPX1 Pro198Leu) were at a significantly increased risk for a multitude of important health outcomes (6). While overall this community in Ecuador did have much higher rates of miscarriages (spontaneous abortions) and birth defects than typical, genomic analysis showed that this risk was tremendously variable based on these two critical glutathione detox pathways. For individuals with 2 variants in the GSTP1 pathway responsible for toxin conjugation (approximately 11.5% of the population), the odds of having a miscarriage or child with a birth defect was 4.9× higher than those who had two copies of the normal (major allele or wild type) GSTP1 variant. For individuals with two variants in GPX1 that conveys significant difficulties in clearing oxidative stress (2 copies of this minor allele found in approximately 7–20% of population depending on ethnicity), the odds ratio jumped to 8.5× higher (6). Both genetic variants are also correlated to a significantly higher risk of mercury toxicity (11). GPX1 also relates to problems with visual memory, increased risk of ulcerative colitis, Type 2 diabetes and peripheral neuropathy risk (12), and bladder cancer risk (13), with the risk being modulated heavily by the level of pesticide/herbicide exposure (14).

The same GSTP1 variant discussed above was also shown to correlate with increased DNA damage with exposure to pesticides in fruit growers in a Chinese study published back in 2006 (15). GSTP1 is also responsible for protecting macrophages from nitric oxide cytotoxicity. Nitric oxide is part of air pollution from traffic and has been associated with sensitization to other inhaled and even food allergens. Children with the higher risk genotypes (Ile105Val/Val105Val) had 2.4× the risk of having food and environmental allergies when exposed to high traffic/high air pollution situations (16).

But the effects of toxicants are not just limited to those who are genetically vulnerable due to poor detox pathways.

GSTT1 and GSTM1 null deletions in mercury and toxin clearance

As previously discussed, GSTP1 is a vital component of the detox system via attaching toxicants, carcinogens and other offending substances to glutathione so they can be eliminated in the urine, feces or sweat (Figure 1). GSTT1 and GSTM1 are also members of this GST (glutathione S-transferase) gene superfamily and are heavily involved in our glutathione conjugation detox system. These 2 genes are unique in that a large percentage of the population is without the protein product due to having a complete deletion of the gene (17). When the gene is absent on both the chromosomes inherited from an individual's mother and father, it is called a GSTM1 or GSTT1 null individual. Those that have the null genotype lack enzyme activity for the respective gene (17) and thus have impaired detox/toxicant clearance (12) as well as impaired heavy metal clearance-

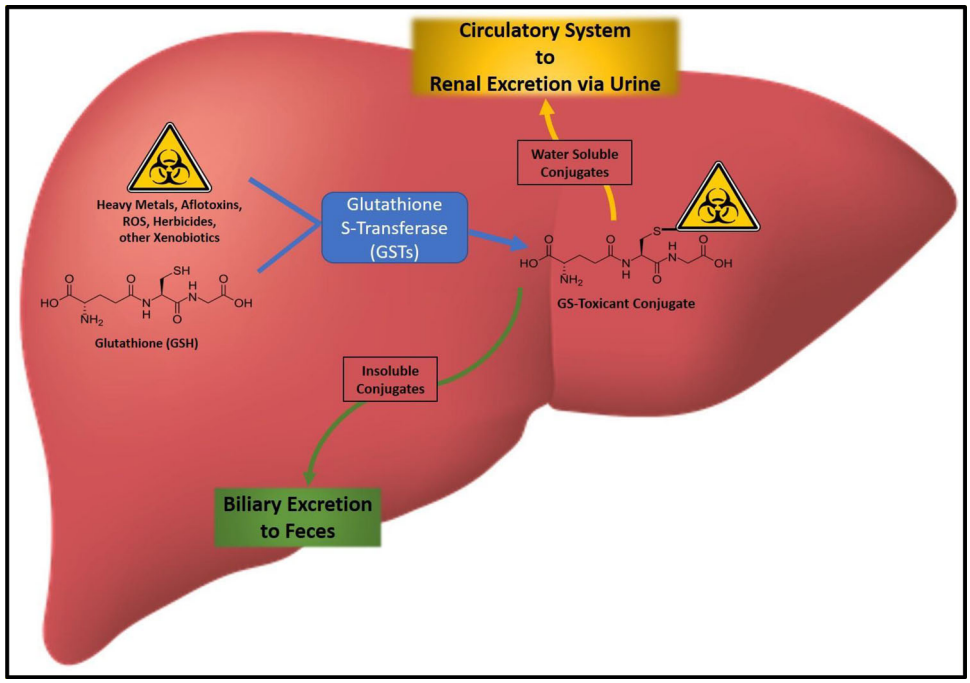

Figure 1. *Glutathione Transferase Conjugation.* Glutathione Transferases in the liver catalyze the conjugation of a variety of toxicants to the cysteine residue of a reduced glutathione (GSH). This conjugate is then excreted ultimately in urine or sweat by way of the circulatory system if water soluble, or in feces via the biliary duct if water insoluble.

including mercury and lead- and enhanced susceptibility to oxidative stress (18).

GSTT1 null, which is found in approximately 17% of the population (can vary by ethnicity) (17), has been shown to increase the risk of a wide variety of serious health issues. Given that glutathione is so central to the removal of various toxicants and the mitigation of their effects, the risk of GSTT1 null can depend heavily on different environmental exposures as well as nutritional factors. These of course vary significantly in different parts of the world. For example, Siberia is known to be one on the most polluted regions of the world with extremely poor air quality due in part due to the spread of pollutants from industrial plants in China, but they also have very high mercury levels due to complex atmospheric and oceanic processes which pushes higher amounts of mercury into the high northern latitudes (19).

In Western Siberia, a maternal GSTT1 null has been associated with 3.63× the risk of congenital malformations in their children, with particularly high levels of cardiac malformations (Odds Ratio or OR = 5.03), urinary tract malformations (OR = 4.20) and CNS malformations (OR = 4.4) (20). In a separate study GSTT1 null was also shown to be associated with a progressive form of epilepsy (OR = 5.44) and the effects were found to be more pronounced when GSTM1 null was also present (21). Regarding GSTM1 null, this deletion has been shown to convey anywhere from 1.34× (22) to 2.06× increased Alzheimer's risk (23). This same study also demonstrated an additive risk when combined with the ε4 allele of the APOE gene, which is known to contribute to inflammatory effects and mitochondrial dysfunction. The risk of Alzheimer's conveyed by the GSTM1 null was 3.07× if present along with one APOE ε4 allele, and up to 5.52× the risk if two APOE ε4 alleles were present (23). Though this article has only gone into detail regarding a few, but the list of further health risks for individuals lacking GSTT1 or GSTM1 function is quite vast. It includes increased risk of various cancers such as lung and brain tumors, neurodegenerative diseases such as Parkinson's, and many other health risks (9, 24).

Addressing glutathione genomic pathways

During clinical training, practitioners are taught that they should not order a test unless they know what they are going to do with the results. This tenant has been used as an example of why clinicians should not yet offer genomic testing to patients. However, with nutritional science, the science of supplementation and a better understanding of genomic mechanisms, clinicians can now use evidence-based medicine to address genomics as part of prevention and targeted treatment regimens.

To help understand this concept of using targeted prevention and intervention strategies, this article will use glutathione pathways as examples. For an intervention to be genomically targeted, it should not only have data supporting that it addresses the genes being discussed, but also outcomes data showing improvement in clinical endpoints affected by the gene. For example, the GSTP1 variant discussed in the examples above has been associated with higher rates of a variety of cancers including breast cancer. Women with GSTP1 Val/Val (2 risk alleles) were shown to have 1.5× the risk of breast cancer and a 1.69-fold increased risk of premenopausal breast cancer. This risk, however, increased further (from 1.5 to 1.75-fold) if these women had a low intake of cruciferous vegetables (25). Thus, recommending a diet high in cruciferous vegetables to GSTP1

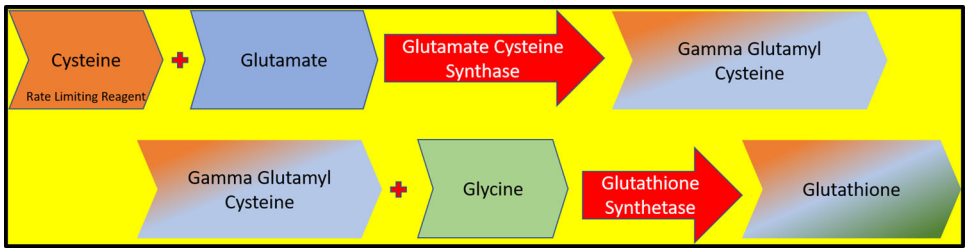

Figure 2. *Glutathione Synthesis.* Glutathione is synthesized in two steps from three amino acids. Initial conversion of Cysteine and Glutamate to Gamma Glutamyl Cysteine (γ-GC) by Glutamate Cysteine Synthase (GCLC) is the rate limiting step due to the relative scarcity of Cysteine. From there, γ-GC is combined with Glycine by Glutathione Synthetase (GSS) to form active Glutathione.

homozygotes makes sense. Research indicates that intake of cruciferous vegetables, which are high in glucosinolates—a sulforaphane producer, has been inversely correlated with breast cancer risk (26). Furthermore, it is known that sulforaphane producers (glucoraphanin and myrosinase in combination) will increase glutathione production via a variety of genetic pathways including the upregulation of GSTP1 (27), and that these same sulforaphane producers have been associated with lower breast cancer risk. Thus, it is reasonable to counsel patients with GSTP1 variants to consider increasing their intake of cruciferous vegetables and/or to supplement with a sulforaphane producing supplement. These dietary and supplementation strategies would be considered genomically targeted. Suggesting supplementation with N-acetylcysteine (NAC), which helps push the rate limiting step for the synthesis of glutathione by providing more available cysteine (Figure 2), would also be another option (28). Interestingly, and fitting with linking recommendations to both genomics and outcomes data, NAC has also been shown to decrease miscarriages (an outcome that was increased in women with 2 GSTP1 variants) (29).

Furthermore, given the studies showing that GSTP1 is involved in the clearance of glyphosates, it also makes sense to counsel these women (especially those who are pregnant or trying to conceive) to do their best to avoid grains and foods highest in glyphosates. Foods containing high levels of allium, such as garlic and leeks, purple sweet potatoes, rooibos tea, honeybush tea, green teas and rosemary extract have all also been shown to upregulate GSTs and it would therefore be appropriate to recommend incorporating as many of these foods into the diet as possible (30). When using food to upregulate gene expression, dosing used in studies needs to be considered as some of the quantities are atypical dietary quantities and supplementation may be preferred (31).

In the case of an individual with variants in the GPX1 pathway discussed previously, sulforaphane and cruciferous vegetables can also be used to upregulate this gene (32), but another highly effective way of upregulating this gene is by increasing the amount of selenium in the diet. This enzyme is known to be a selenoprotein and the level of transcription of this gene relates to selenium status. For individuals with variants in GPX1, increasing dietary selenium (1 brazil nut daily) was shown to upregulate the production of this enzyme significantly (33). Individuals with GPX1 variants have been shown to have worse long-term visual memory skills and other signs of cognitive decline and supplementation with Brazil nuts has been shown to slow this cognitive decline and improve memory.

Vitamin C activation and genomics

Glutathione transferases are involved in other important chemical reactions throughout the body that also contribute to environmentally acquired illness. While sun exposure may not exactly be a classic toxin, high energy blue light and radiation from the sun does cause a lot of oxidative stress to the eyes (34). Pollutants in the air can further contribute to ocular injury. GSTO1 and GSTO2, which are another class of the glutathione transferases, are involved in converting the precursor of vitamin C synthesized by our bodies into active ascorbic acid, an important antioxidant. GSTO1 and GSTO2 variants have been linked to cataracts (35), while a literature search will also show that vitamin C deficiency has been linked to cataracts (36). Therefore, it makes sense in individuals with GSTO1 and GSTO2 variants, especially if homozygous, to recommend vitamin C supplementation or careful attention to make sure that they get adequate vitamin C in their diet as a genomically targeted intervention.

NQO1 and benzene toxicity

While there are many different genes associated with risk of benzene toxicity including CYP2E1 which will be discussed later, but for the purpose of clarity, this article will focus here just on the highly significant NAD(P)H quinone oxidoreductase 1 (NQO1). The NQO1 gene encodes a reductase known to be important for its ability to convert inactive forms of Vitamin E and CoQ10 to their active forms, which are themselves important antioxidants (37). However, within the context of benzene, NQO1 most notably is involved in the reduction of benzoquinones into hydroquinones (Figure 3) (38). Both benzoquinone and hydroquinone are natural stages within the metabolism of benzene and have been associated with toxicity. However, partial or total loss of NQO1 function (and thus greater concentration of benzoquinone) results in more severe benzene toxicity, implicating a lessened toxicity when in a reduced state (hydroquinone). Indeed, this has been confirmed by research, demonstrating the importance of NQO1 to relief of benzene toxicity (39). For those interested, this is hypothesized to be due to hydroquinone's mechanism of toxicity to be indirect via

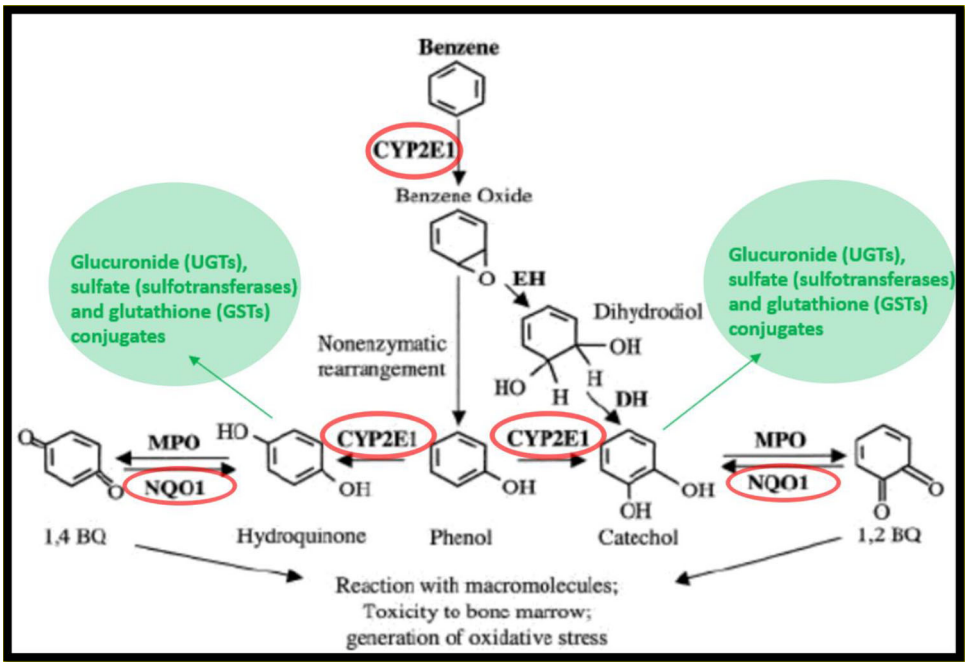

Figure 3. *Benzene Metabolism.* Benzene is metabolized in a series of steps catalyzed by various enzymes including CYP2E1, Myeloperoxidase (MPO), Epoxide Hydrolase (EH), and NQO1. NQO1 plays a critical role in converting the highly toxic benzoquinones back into the less toxic and more readily conjugated hydroquinones. Adapted from diagram courtesy of Dr. Brian Cornblatt, PhD.

creation of ROS (and thus addressable by alternate pathways), while benzoquinones directly damage biological molecules such as DNA, and are difficult to attenuate through alternate mechanisms (38, 40).

Genetic variants of NQO1 at C609T (the most commonly studied variant) often lead to complete or near complete loss of function for each chromosome they are on (41). Thus, if an individual has one minor allele, they are only at 50% of normal NQO1 function, while with two copies they are at nearly 0% functionality. These individuals are at much higher risk for adverse effects from benzene exposure. In research conducted among the population of Shanghai, homozygotes for the C609T variant were found to be at a 7.6× increased risk for benzene poisoning, which was linked to later development of nonlymphocytic leukemia (42).

In cases of partial or complete loss of function of NQO1, a few interventions have been noted to help reduce damage from benzenes. The most ideal interventions seem to involve restoring NQO1 function to normal levels. Particularly in heterozygotes expressing half function, sulforaphane (broccoli, kale, cabbage, etc.) in moderation has been demonstrated to restore apparent full function in *in vitro* studies (43). Similar effects have been demonstrated in response to carnosic acid, commonly found in rosemary (44), and alpha lipoic acid (45). Furthermore, sulforaphane and alpha lipoic acid have been shown directly to diminish the effects of benzene toxicity, confirming the biological significance to the upregulation of NQO1. Further studies on the benzene-protective effects of carnosic acid are thus warranted, but currently no such effect has been demonstrated. What these supplements have in common is an apparent activation of the Nrf2 pathway upstream of NQO1 (43–45)—providing a target of upregulation that may be addressed by yet other supplements or dietary changes. However, it is unclear if these interventions can restore sufficient function in the cases of those with variants in both copies of the gene, and so in those rare cases extra care should be taken to avoid benzenes. For these individuals with partially or fully impaired NQO1 pathways, there may be benefit found in pushing glutathione pathways or providing oral glutathione. One intermediate metabolite of benzene (benzene oxide) has been demonstrated to conjugate with glutathione for efficient removal and deactivation of this product (46) however this has not yet been studied as a sufficient mechanism in terms of significantly alleviating benzene toxicity.

Pesticide exposure and genomics

Pesticides are removed by various processes depending on the type of pesticide. Pesticides are considered "environmental neurotoxicants" (47). One of the most famous pesticide pathways is the PON1 gene pathway which encodes the enzyme paraoxonase 1. This protein is involved in hydrolyzing organophosphorus insecticides. In a study of individuals with very high environmental or occupational exposure (exterminators and those spraying crops with pesticides) to various PON1 metabolized pesticides, there was a 1.9–2.7× increased risk of macular degeneration. This fits with the fact that variants in PON1 have been associated with increased risk of organophosphate toxicity, macular degeneration, as well as with a number of other health issues (47). For individuals with known significant variants in the PON1 pathway there are many genomically targeted potential interventions. Advising them to use organic produce for at least the "dirty dozen" can decrease their exposure to these organophosphates. Additionally, quercetin (48), astaxanthin (49) and pomegranate (50) have been shown to upregulate PON1 expression. Nutritionally, avoiding high

fructose corn sirup which decreases PON1 expression, and increasing the consumption of pomegranate juice can be beneficial and in one study the equivalent of 2 oz of pomegranate juice was shown to increase PON1 activity by up to 83% (50).

CYP450 system and toxicity

While this review does not have time to do a full discussion of the Cytochrome P450 (CYP450) system, an evaluation on the genomics of clearance of environmental toxicants would not be complete without a discussion of this system. Cytochrome P450s are heavily expressed in the main organs responsible for removing toxicants including the liver, kidney and GI tract, but are also components of the blood-brain barrier (51). CYP450 enzymes are important for what is known as "Phase I metabolism", which means they are responsible for making compounds more water soluble so they can effectively be eliminated by the kidneys. CYPs catalyze various reactions such as hydrolysis, oxidation and reduction that are involved in the metabolism of xenobiotics (foreign substances) including drugs, chemicals and pollutants as well as in the metabolism of hormones (52). There are many different CYP450s that are denoted with a series of numbers and letters. However, in the context of a discussion of environmental toxicants, CYP1B1 and CYP2E1 are of particular importance as they catalyze the conversion of many environmental toxicants into carcinogens and contribute to other diseases because of their role in lipid peroxidation. These two enzymes (along with CYP1A1 and CYP2D6) are not only found in the liver but have also been found in significant amounts within the mitochondria. Thus, individuals harboring CYP1B1 variants that ***increase*** the expression of these enzymatic pathways have the associated increased risk for adverse health outcomes. This is an important concept of genomics to understand. In addressing genomic variants, an understanding of function and relation to health risks must first be considered prior to deciding whether to upregulate or downregulate activity. As one can imagine foods, supplements, medications and toxicants can differentially up ***and*** downregulate enzymatic functions.

Some of the compounds metabolized by CYP1B1 include polycyclic aromatic hydrocarbons (PAHs), which have multiple benzene rings hooked together in their backbone. PAH exposure comes from the combustion of coal, oil and other biofuels (even from the burning of wood and other organic materials) (53). In first world countries where people do not tend to cook over coal or wood burning stoves, exposure comes from smoke (including secondhand smoke) as well as from grilling and smoking meat (54). Heterocyclic amines (HAAs) contain a benzene ring and a nitrogen (amine) containing group. Niacin (vitamin B3) is a heterocyclic amine, but carcinogenic heterocyclic amines are generally formed when protein foods (meats, etc.) are cooked at a high temperature (55). An abundance of heterocyclic amines are also released from tobacco when it is smoked (56).

Another CYP1B1 substrate, N-nitrosamines are created as part of a reaction between nitrogen oxide and secondary amines. Nitrites, which are used as food preservatives—particularly in processed meats, generate these potentially carcinogenic compounds or "pro-carcinogens." When these substances are enzymatically cleaved by CYP1B1, they become carcinogenic and can induce mutations in proto-oncogenes and tumor suppressor genes and result in DNA damage (57). CYP1B1 mediated increases in lipid and protein peroxidation also can contribute to significant tissue damage since lipids are an essential part of the membranes of cells. Lipid peroxidation has been implicated in cardiac disease, hypertension, inflammatory bowel disease, bipolar disorder, asthma and neurodegenerative diseases to name a few (58–62).

Many natural flavonoids such as naringenin (63), resveratrol and pterostilbene have been shown to decrease CYP1B1 expression (64, 65). In fact, synthetic stilbenes are being studied as potential drugs because of their ability to decrease endpoints like tumorigenesis and cancer, hypertension, atherosclerosis, and even obesity (66). Foods that are high in naringenin, resveratrol and pterostilbene (such as citrus, red grapes and blueberries), along with the corresponding supplements, may be beneficial to individuals with overactive CYP1B1 pathways due to genomic variants. While this article has addressed how CYP activities can be both negatively and positively impacted by environment, diet, and supplementation, there are other lifestyle changes that can also help decrease risk. For example, some of the CYP1B1 variants associated with increased activity have been shown to increase the risk of laryngeal cancer (OR = 2.65). The odds ratio doubles when combined with smoking (OR= 5.8). When combined with alcohol, the risk is also quite high (OR = 4.5) (67). Therefore, counseling these individuals about the dangers of tobacco and alcohol becomes an essential part of health promotion.

CYP2E1 is also involved in toxin metabolism, with the by-product of CYP2E1 activation being reactive oxygen species. Alcohol indirectly upregulates CYP2E1 which then leads to more ROS formation. Genetic variants in CYP2E1 that upregulate its transcription can heavily contribute to alcohol induced liver fibrosis risk as well as inflammation (68, 69). This enzyme is also involved in the metabolism of benzene and acrylonitrile, which is used extensively in the production of plastics. While CYP activity in the brain is roughly only 1% of that in the liver, CYP450s also appear to be important contributors to brain pathology and inflammation. Though not yet confirmed in human studies, chronic low dose exposures to acrylonitrile compounds have been associated with glial cell activation and inflammation in animal models (70). Furthermore, nicotine and alcohol both upregulate brain CYP2E1, which increases ROS formation mainly in the form of superoxide and hydrogen peroxide (71).

Again, while counseling CYP susceptible individuals to avoid "upregulating toxicants" is beneficial, other interventions—such as maintaining adequate levels of enzymatic antioxidants, vitamins (A, C, E), glutathione producers, beta carotene, and alpha lipoic acid—can be of great help. While many interventions are focused on treatment of ROS and

CYP induced damages, some of these interventions, such as vitamin E, have also been shown to decrease CYP2E1 expression (71). Additionally, hydrogen water has studies showing it can help to remove ROS and has effects on the brain and cognition (thus implicating its ability to cross the blood brain barrier) (72). Therefore, it would be another potential intervention for those with overactive CYP2E1 pathways. Studies showing that depletion of glutathione increases the toxicity of CYP2E1 overexpression and that CYP2E1 inhibitors decrease the toxicity (71) fit with maintaining ideal glutathione levels in individuals with higher CYP2E1 expression.

Conclusion

Our genetic code accounts for various pathways paramount to our innate ability to remove toxicants. While individuals who are homozygotic for various impairments are the minority of the population, significant homozygous variants still cumulatively account for over a third of the population. These genomically vulnerable individuals serve as "canaries in the coal mine." They demonstrate the detrimental significance of the chemicals society is exposed to in this new and modern world. These toxicants influence the disease burden of cancers, congenital malformations and chronic illness, particularly for those at genetic risk but for all individuals at sufficient levels. One course of action clinicians can take is to help patients understand their own genomic risks and address their personalized needs through genomically targeted dietary and supplement recommendations. Clinicians, with the help of genomics, can advise patients to avoid food with pesticides, glyphosates, higher mercury and arsenic levels, benzene and other toxicants, but also to increase foods that specifically push their impaired detox pathways such as brazil nuts, cruciferous vegetables, and pomegranate and to supplement with sulforaphane, glutathione, vitamin C and others.

The field of medical genomics is still relatively young and, while already quite beneficial to the field of personalized medicine and nutrition, there is still a tremendous amount of research to be done. With so many genes involved in the removal of toxins and toxicants and an ever-evolving multitude of toxicants in the environment, a nearly infinite array of combinations of genetic code and environmental stressors arises for future research. Of particular note might be longitudinally evaluating many of these naturally occurring interventions, which have demonstrated benefits on acute enzyme levels or activity, on real outcomes in genetically compromised individuals- particularly those already at risk due to geography or occupation.

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