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Glutathione S-Transferase Gene Associations and Gene-Environment Interactions for Asthma

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Abstract

Purpose of Review Asthma is one of the most common chronic inflammatory airway diseases. Airway oxidative stress is defined as an imbalance between oxidative and antioxidative processes in the airways. There is evidence that chronic damage caused by oxidative stress may be involved in asthmatic inflammation and reduced lung function. Given their biological antioxidant function, the antioxidant genes in the *glutathione S-transferase (GST)* family are believed to be associated with development and progression of asthma. This review aims to summarize evidence on the relationship between *GST* gene polymorphisms and asthma and interactions with environmental exposures.

Recent Findings The current evidence on the association between *GST* genes and asthma is still weak or inconsistent. Failure to account for environmental exposures may explain the lack of consistency. It is highly likely that environmental exposures interact with *GST* genes involved in the antioxidant pathway. According to current knowledge, carriers of *GSTM1(rs366631)/T1(rs17856199)* null genotypes and *GSTP1 Val105* (rs1695) genotypes are more susceptible to environmental oxidative exposures and have a higher risk of asthma. Some doubt remains regarding the presence or absence of interactions with different environmental exposures in different study scenarios. The *GST*-environment interaction may depend on exposure type, asthma phenotype or endotype, ethnics, and other complex gene-gene interaction. Future studies could be improved by defining precise asthma endotypes, involving multiple gene-gene interactions, and increasing sample size and power.

Summary Although there is evidence for an interaction between GST genes, and environmental exposures in relation to asthma, results are not concordant. Further investigations are needed to explore the reasons behind the inconsistency.

Keywords Reviews · Asthma · Gene polymorphism · Oxidative stress · Glutathione Transferase · Gene-environment interaction

Introduction

Asthma is the one of the most prevalent chronic non-communicable diseases, characterized by airway inflammation and reversible airway obstruction. There is a large body of evidence implicating increased airway oxidative stress as a driver for asthma [1]. Oxidative stress reflects the endogenous imbalance between the overproduction of oxidants in terms of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and relative underproduction of antioxidants [1]. There are many exogenous sources of ROS and RNS, such as cigarette smoke, air pollutants, metals, mold, and some medications. These ROS and RNS play an important role in the pathogenesis of inflammatory conditions. After exposure to environmental triggers, normal physiological antioxidant defense mechanisms are usually able to eliminate ROS and prevent airway damage or reduce oxidative stress to allow repair. These mechanisms involve antioxidant enzymes including superoxide dismutase (SOD) and glutathione (GSH), which can detoxify a wide range of environmental exposure induced oxidants. However, when the capacity of endogenous antioxidant defense mechanisms decreases, our body is not able to compensate for overproduction of ROS/RNS. This mechanism of imbalance between ROS, RNS and antioxidants is a long-term continuous and dynamic process and may explain the development and progression of asthma [1].

Glutathione S-transferases (GST) encoded by the *GST* gene family catalyze the conjugation of electrophilic compounds to GSH. Their catalytic function makes these enzymes

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crucial to the detoxification of a wide range of exogenous compounds [2••]. Considering the pertinent biochemical function of these antioxidant enzymes, the association between *GST* genes and asthma risk has been extensively studied, especially for three isozymes: *GSTM1*, *GSTT1*, and *GSTP1*. Gene polymorphisms affect the activity of these isozymes: gene deletion polymorphisms commonly occur in the *GSTM1(rs366631)* and *GSTT1(rs17856199)* genes, whereas, two functional sequence variants in *GSTP1* single nucleotide polymorphisms (SNPs) based on substitutions at codon 105 (Ile105Val, rs1695) and codon 114 (Ala114Val, rs1138272). The *GSTP1*, Ile105Val substitution may contribute to oxidative stress susceptibility and airway inflammation [3], however the effect of the *GSTP1* Ala114Val substitution is less studied [4•]. Broader studies have focused on the direct influence of the entire family of *GST* genes on the respiratory system, and also whether theses genetic susceptibilities affect asthma risk only when exposed to environmental factors [5••]. Understanding the associations between *GST* genes and asthma development and specific asthma phenotypes will provide insight into mechanisms of asthma development, severity and disease progression, as well as help to develop personalized therapies for susceptible people. In light of the clinical and epidemiological importance of asthma and potential benefits of further research into its etiology, this review will provide an overview on the current understanding of the role of *GST* and *GST*-environment interactions in asthma development.

Overview of GST Genes

GST genes are a supergene family that code for enzymes which detoxify ROS and RNS, thus defending tissues against oxidative stress [6, 7•]. The level of *GST* gene expression is particularly important in determining the resultant enzyme levels available to assist with detoxification of chemicals and xenobiotic compounds [8]. In the process of detoxification, glutathione firstly binds with ROS or xenobiotics, and then GST enzymes catalyze the conjugation of glutathione with RNS/ROS and xenobiotics, in order to convert them to less reactive and more water-soluble compounds. Finally, the detoxified water soluble compound is eliminated from the body (Fig. 1) [8, 9]. *GST* enzymes have been widely studied as potential biomarkers for oxidative stress related to environmental exposures [8, 9]. There are seven classes of the GST gene superfamily: alpha, mu, pi, sigma, theta, omega, and zeta, but the three main classes that have been extensively studied are pi (*GSTP*), mu (*GSTM*), and theta (*GSTT*). In this review, we only focus on these three main classes.

GSTP1 There is only one isoform identified for *GSTP*, called *GSTP1*, which is located on chromosome 11q13. *GSTP1* is the most common form of GST found in the respiratory tract lining fluid, responsible for over 90% of *GST* enzyme activity [7•]. *GSTP1* has complex genetic variation and haplotypes in terms of 4 alleles identified as *GSTP1**A (Ile105-Ala114), *GSTP1**B (Val105-Ala114), *GSTP1**C (Val105-Val114) and *GSTP1**D (Ile105-Val114) [4•]. In terms of the amount of active *GST* enzymes in relation to the most common polymorphism of *GSTP1* (Ile105Val), the homozygous wild genotype (Ile105) has the highest level of enzyme activity, while the homozygous mutant genotype (Val105) has the lowest activity [10].

GSTM1 The *GSTM* class is located at a 97-kb region on chromosome 1p13. There are five isoforms within the GSTM family. Though all *GSTM* gene isoforms have specific functions and should be considered separately for health outcomes, only the *GSTM1* isoform polymorphism has been well studied so far.

GSTT1 The *GSTT* class is located on chromosome 22q11 and there is only one isoform called *GSTT1*.

Unlike *GSTP1*, the *GSTM1* and *GSTT1* polymorphisms are usually evaluated in terms of the presence or absence of homozygous deletion (present or null genotype). People with null genotypes have complete loss of enzyme activity resulting in a reduction of antioxidant capacity.

The Link Between *GSTP1/M1/T1* and Asthma: Inconsistent Findings

Although there is a good biological rationale for a relationship between GST genes and respiratory health, the current evidence is still weak or inconsistent. The most commonly studied *GST* gene in relation to asthma outcomes is *GSTP1*, but the evidence for *GSTP1* risk alleles is inconsistent. Current studies have focused on the Ile105Val substitution rather than haplotypes because enzymes with Ala114val have lower allele frequencies [4•, 11] and there is little evidence of association of Ala114val with respiratory health in previous studies [12, 13]. As *GSTP1* with Ile105 genotypes has the highest enzyme activity, carriers of *GSTP1* with any Val105 alleles would be expected to have a higher risk of respiratory symptoms. There is some support for this hypothesis. A case control study in Turkey found that subjects with *GSTP1* homozygous Val105 genotypes had a 3.55 fold increased risk of atopic asthma in adulthood compared to those with homozygous Ile105 genotypes [14]. A Spanish population-based birth cohort study found that 6-year-old children with *GSTP1* Val105 genotypes had an increased risk of wheezing compared to those with Ile105 genotypes. Furthermore, the risk appeared to be dose dependent with respect to the number of Val genotypes, with an intermediate risk for children with *GSTP1* Ile105Val genotypes [15••]. However, a greater

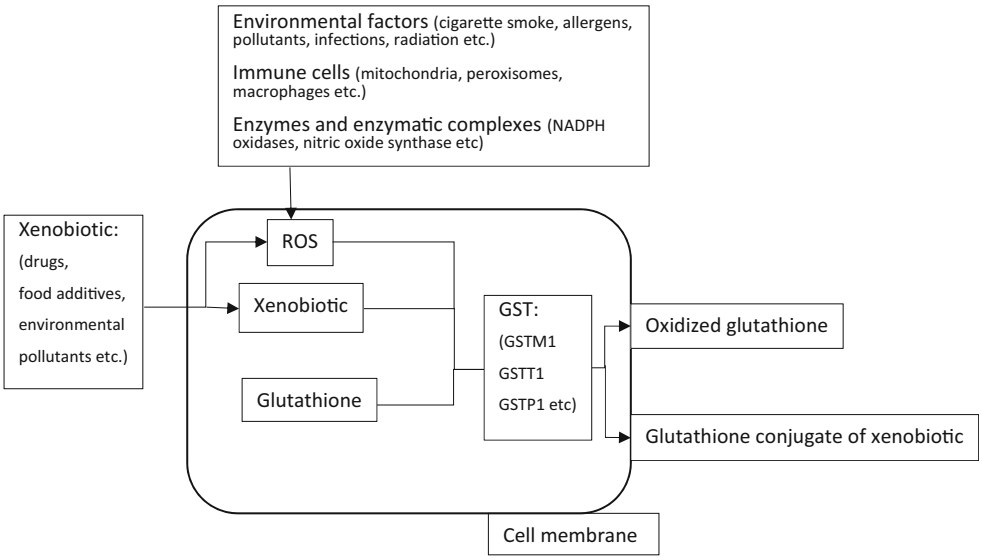

Fig. 1 Glutathione neutralizes xenobiotics and ROS with the help of GSTs

number of studies have found the opposite relationship. A UK study conducted on adults reported that having the *GSTP1* homozygous Val105 variant was associated with a six-fold lower risk of asthma compared with homozygous Ile105 carriers [4•]. A case-control study in Pakistan also found that carriers of *GSTP1* with Val105 genotypes were more frequently found in the non-asthmatic population than in people with asthmatic [16]. Other studies have also found a protective effect of the *GSTP1* homozygous Val105 genotype on asthma phenotypes in Egyptian children [17], the Swiss general population [18] and Japanese patients with COPD [13]. Moreover, not all studies found an association between *GSTP1* genotypes and asthma. A German study did not find evidence that *GSTP1* polymorphisms played a major role in the development of bronchial asthma in children [19].

Overall, there is some evidence that people with *GSTM1* null and *GSTT1* null genotypes are more likely to develop adverse respiratory outcomes [20, 21] though there is still some inconsistency. A case control study in Turkey conducted on patients hospitalized for asthma and healthy volunteers (controls) found that asthma patients had a higher prevalence of both *GSTM1* null genotypes, and *GSTT1* null genotypes than controls [14]. Similar case control studies were also undertaken in Russia [22], Iran [23] and China [24] to identify potentially adverse effects of *GSTM1* and *GSTT1* null genotypes on asthma outcomes. Although all these studies found associations between null genotypes and increased asthma risk, they were all small studies with sample sizes of less than 300 participants. In contrast, two large cohort studies, the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) [18] (n=4422), and ALSPAC [15••] (n=7262) in the UK, did not find evidence of associations between *GSTM1* or *GSTT1* null genotypes and asthma.

In 2013, a meta-analysis was conducted on 43 papers, including studies in both adults and children, and found no evidence for associations between *GSTM1* or *GSTP1* polymorphisms and asthma susceptibility [2••]. However, there was evidence that *GSTT1* null genotypes were associated with increased risk of asthma (pooled OR 1.33, 95%CI 1.10, 1.60), but high heterogeneity (I^2= 74.7%) was identified in these analyses that combined different study designs, populations and vastly different asthma definitions [2••]. Another review and meta-analysis, conducted in 2010, summarized the evidence for an association between GST genes and asthma phenotypes and did not support a substantial independent role of GST genes in the development of asthma [15••].

There are several possible reasons for this lack of evidence to support associations. Firstly, people may have overlapping *GSTM1*, *GSTT1*, and *GSTP1* de-functional and beneficial polymorphisms, such that a deficiency in one isoform may be compensated for by another. Conversely, the combination of multiple GST risk genotypes may have an additive effect on respiratory health outcomes. To explore this, the same meta-analysis included 14 additional studies on adults and found a higher risk of asthma for people with *GSTM1* null and *GSTT1* null together compared to those with two non-null genotypes, but no evidence of an association in those with only one null *GSTM1* or *GSTT1* gene [15••].

Failure to account for environmental exposures may also partially explain the lack of consistent, strong evidence for an association between *GST* genes and asthma. Both meta-analyses suggested that future studies of large sizes should focus on *GST* genes in conjunction with environmental oxidative exposures [2••, 15••]. The presence of gene-environment interactions may help to explain the inconsistency in face of the strong biological plausibility.

GST-Environment Interactions in Asthma: Less Inconsistent

The most frequently evaluated *GST*-environment interactions on asthma include exposure to tobacco smoking, outdoor air pollutants, and household exposures. The majority of studies investigating *GST* genes, environmental exposures and asthma-associated phenotypes suggest that the risk of asthma is not either purely genetically or purely environmentally driven. Instead, increased asthma risk results from the combination of a toxic environmental exposure augmented by genetic susceptibility.

Tobacco Smoke

This is the most studied environmental exposure with respect to *GST* interactions and asthma in humans. The overall evidence supports the hypothesis that *GSTM1*/*T1* null genotypes predispose individuals to the adverse effect of smoking. One of the earliest studies that investigated *GSTM1* interactions, conducted in the US in 2002, found an association between in utero exposure to maternal smoking and increased risk of childhood asthma and wheezing that was observed only in children with *GSTM1* null genotypes [25]. Another study on school age children in Germany extended these findings to support a relationship with current exposure to environmental tobacco smoke (ETS) in childhood. The authors found that children who were living in a household with a heavy smoker (>20 cigarettes per day) had increased risk of current asthma, current wheeze, ever wheeze and shortness of breath but only in those with *GSTM1* null alleles and not in similarly exposed children with *GSTM1* present alleles, although the statistical evidence for an interaction was not strong (All p values are over 0.5) [26]. A cross-sectional study also found evidence that increased risk of asthma, asthma symptoms and wheezing was apparent only in children who had a *GSTM1*/*T1* null genotype and were also exposed to current ETS [26]. Interestingly, a Taiwanese study provided conflicting evidence of a borderline protective association between *GSTM1* null genotypes and decreased risk of asthma when children were exposed to ETS (p=0.0573) [27].

Findings are least consistent for *GSTP1*, although it is the most commonly studied of the three mentioned GST genes. Most studies investigating the interaction between *GSTP1* and tobacco smoke exposure found that having *GSTP1* with Val105 alleles was associated with increased risk of asthma/wheeze outcomes in children who had been exposed to tobacco smoke in utero [28–31]. In contrast, a Korean study conducted three-way interactions between *GSTP1*, vitamin A and ETS, and found evidence that school-age children with exposure to ETS and low vitamin A levels had an increased risk of asthma diagnosis compared to children who did not have these two risk factors and this association was only significant in *GSTP1* Ile105 alleles but not Ile105Val or Val105 alleles [32]. Moreover, several studies showed no evidence of an interaction for *GSTP1* genotypes and tobacco smoke exposure on asthma risk. A birth cohort study found no interactions between *GSTP1* polymorphisms and ETS exposure on persistent wheezing for infants at both 12 and 24 months of age [33]. A case-control study in Northern Mexico found no associations between *GSTP1* polymorphisms, childhood asthma and ETS [34]. A recent birth cohort study did not find an interaction between *GSTP1* polymorphisms and early life tobacco smoke exposure on asthma in adolescence [35].

Outdoor Air Pollution

Interaction between different air pollutants (e.g., NO_2, ozone, particulate matter $(PM)_{10}$, and $PM_{2.5}$) or other traffic-related air pollution measures (e.g., distance to major road), and GST variants on childhood asthma risk has been a major focus in the field [36•]. The potential interaction of *GSTM1*/*GSTT1* genes on the relationship between outdoor air pollution exposure and asthma has been less explored compared to tobacco smoke. Bowatte et al. found that increased exposure to major roads in 100 m buffers around the home during the first year of life was associated with increased asthma or wheeze at the age of 12 years in carriers of *GSTM1* non-null and *GSTT1* null alleles [37]. In addition, Bowatte et al. provided the first evidence on effect modification by GST polymorphisms in adults, suggesting associations between living less than 200 m from a major road and increased risk of asthma and wheeze only in those with *GSTT1* null genotypes [38]. No interactions were found for *GSTM1* or *GSTP1* polymorphisms [38].

There was some evidence suggesting a relationship between the *GSTP1* minor allele (Val105 or Ile105Val) and increased risk of asthma when exposed to outdoor air pollution. A study combining 6 cohorts comprising 5115 children aged 7–8 years found that carriers of *GSTP1* with any Val105 alleles had an increased risk of current or ever asthma when exposed to higher levels of NO_2 during the first year of life compared to those with Ile105 alleles [39]. The Taiwan Children's Health Study (TCHS) also showed that children with *GSTP1* Val105 alleles had increased risk of asthma or wheeze when exposed to higher levels of $PM_{2.5}$, ozone [40], and PM_{10} [41].

Household Exposures

Several studies have investigated interaction between GST genes and diverse household exposures and asthma risk. These exposures include smoke from incense burning [42], wood stoves, candles [43], and mold [33]. However, only

one of these studies identified interactions, finding that the frequency of incense burning was associated with an increased risk of current asthma, asthma medication use, lifetime wheeze, nocturnal wheeze and exercise wheeze in children with *GSTT1* null genotypes. These associations were not seen in those with *GSTT1* present genotypes [42].

Reasons for Inconsistent Findings in the *GST*-Environment Interactions and Respiratory Outcomes

Asthma Phenotype Definition The underlying causes, inflammatory processes and clinical symptoms for asthma can vary from patient to patient, and even change over time in the same patient. For this reason, it is widely believed that "asthma" is an umbrella term describing a collection of respiratory diseases with different phenotypes, rather than a single disease. One reason for the lack of consistent associations found for exposure-GST interactions and asthma risk may be related to most studies using oversimplified asthma phenotypes (e.g., "physician diagnosed asthma") when asthma is such a heterogenous disease. Not all studies confirmed asthma with objective measurement (e.g., bronchodilator response, methacholine challenge confirmation etc.). There is likely misdiagnosis of asthma in some studies, potentially leading to inconsistency in the results. Non-standardized asthma definitions mean that the results from different *GST* interaction studies may not be comparable. Although there is likely substantial overlap in the individuals identified by each definition, it is important to recognize the variety of methodologies used in epidemiological studies as this may explain some inconsistency in the results and help us to better understand the relationship between asthma and potential risk factors in different settings.

Timing of Exposure and Outcome Antioxidant capacity varies with age, thus the magnitude of gene-environment interaction may also change over the lifetime. Age was found to be involved in gene-environment interaction. A cross-sectional study in Scotland found evidence among asthmatic children aged 13–21 years that having a *GSTM1* null genotype may negatively influence lung function. There was no similar interaction found for children aged 3–13 years [20]. Moreover, a recent review suggested that *GST* interactions are more important in childhood compared to adulthood [5••]. This may due to antioxidant defenses playing a crucial role for childhood respiratory health by detoxifying environment toxins [5••]. Children's lungs are still developing and therefore more susceptible to environmental exposures. In addition, immune responses are relatively naïve in children compared to adults.

GSTP1 Haplotype When considering *GSTP1* polymorphisms, though the evidence generally showed that carriers of the *GSTP1* Val105 genotype had less risk of asthma when exposed to environmental factors, there were also contradictory findings in the literature [5••, 36•]. Thus, it is difficult to draw a firm conclusion on *GSTP1* risk alleles. One of the reasons for this lack of consistency could be that this polymorphism was investigated as SNPs, not haplotypes. The majority of papers have focused on the Ile105Val substitution because the minor Ala114Val allele has a lower frequency. Limited evidences suggested that people with *GSTP1* Ala114 genotypes had increased risk of atopy compared to those with Ala114Val and Val114 [12]. However, *GSTP1* has a more complex genetic variation than *GSTM1* and *GSTT1*, and has recognized haplotypes, in terms of 4 linked SNPs. Many of the studies had small numbers so were unable to address *GSTP1* using these 4 distinct haplotypes, SNP-SNP interactions, or background variation effects. There is some evidence that the *GSTP1* Ala114Val polymorphism influences the activity of the *GSTP1* Ile105Val substitution [3]. Therefore, haplotypes may be a better measure of genetic exposure [44]. Evidence suggested that individuals having a Val in the 105 position along with an Ala allele in the 114 position exhibited a stronger catalytic efficiency compared to individuals with the Val allele in the 105 position but lacking the Ala allele in the 114 position [44].

Complex GST and Other Antioxidant Pathway Genes Though *GST* genes appear to be important in asthma etiology, the evidence regarding main effects and interactions was inconsistent. These ambiguous findings may reflect the complexity of the human antioxidant biologic pathways involved in detoxification of potentially harmful environmental exposures. There are several antioxidant pathway genes that have been identified as potentially important for lung health including *NAD(P)H dehydrogenase [quinine] 1 (NQO1)* and *heme oxygenase 1 (HMOX-1)* [7•]. The effect of each antioxidant gene individually may be very small and difficult to detect. It is also likely to be dependent on the presence of other antioxidant genes. For instance, Li et al. found that children carrying *GSTM1* null and *NQO1* ser genotypes were at increased risk of asthma when exposed to tobacco smoke, but not in the unexposed group and that *GSTM1* alone was not associated with asthma in both exposed and unexposed groups [27]. In addition, nutrients, especially vitamins, have antioxidant properties and may play a role in asthma pathogenesis, along with *GST* genes. A South Korean study suggested that supplemental nutrition intake, like vitamin A, could enhance antioxidant capacity and possibly prevent respiratory harm in susceptible children with risk *GST* genotypes exposed to ETS [32].

Genetic Profiles for Ethnicity Most studies have not considered the role of genetic ancestry on asthma outcomes. Gene-environment interactions may be specific to individual ethnic groups [45]. It is known that the frequency of GST variants

differs between ethnic groups. The frequency of Val105 in *GSTP1* varies from 14% (95% CI 9, 19) in Asians to 32% (95%CI 31, 33) in Europeans [7•]; The prevalence of *GSTM1* null genotypes shows ethnic variation from 23 to 41% for African descent, 32 to 53% for Asian descent, and 35 to 62% for European descent [46]. *GSTT1* null genotypes are more prevalent in Asians, ranging from 38 to 58%, than among those of European ancestry (15–31%) and African descent (22–29%). The prevalence of *GSTT1* null is lowest in Hispanic populations (10–12%) [46].

Future Direction of *GST* Studies

Toward a Precise Endotype Definition A further step toward determining more precise knowledge of asthma etiology, involves addressing the concept of asthma endotypes in *GST* studies. This involves defining asthma by clinical characteristics (phenotypes), as well as molecular and pathogenic features, resulting in "asthma endotypes." *GST* enzymes coded by *GST* genes influence antioxidant biomarker levels, so they may be related with asthma progression at a pathologic level. Different endotypes will likely better characterize distinct forms of asthma, and will probably have different environmental and genetic risk factors [47, 48]. A *GST*-environment interaction study from The Avon Longitudinal Study of Parents and Children (ALSPAC) acknowledged that phenotypes derived from symptoms and their age at onset cannot fully characterize asthma into classes that represent distinct etiologies and prognoses. Hence, it is the important to consider asthma endotypes. Another large population-based cohort study in the UK identified four phenotypes of adult asthma that were characterized by discordance between symptoms and eosinophilic inflammation (endotype) [49]. These studies emphasize the need for new approaches for classification of asthma endotypes.

Take into Account Multiple Risk Variants So far, over 70 variants in candidate genes have been found to be associated with phenotypes of asthma [50], including the *β2-Adrenergic Receptor*, *IL-4, IL4 Receptor α*, *CD14, β chain of the high-affinity IgE receptor*, *TNF-α*, and the *α1-antitrypsin* gene [51]. However, in many cases, the findings are limited. Some genetic variants have shown evidence of increased risk, but the magnitudes of risk were moderate. Many genes may have an association with asthma but were not detected, suggesting the potential multiplicative effect of multiple risk variants should be taken into account. An important goal of the further studies on gene-gene or gene-environment interactions is to identify a group of variants that will reliably predict the risk of susceptibility or progression of asthma.

Increase Sample Size and Power Future studies should consider sample size and power. Cooperation between studies and investigators is necessary to establish large gene-environment interaction studies. Moreover, the power can also be enhanced by reducing the misclassification of measures by using better measures of exposures and outcomes. For instance, many studies have investigated tobacco smoke exposure by self-report from questionnaires, not from objective measurements like urine cotinine levels. Lung function, as an objective outcome measure and continuous variable, has more power to find evidence for an association when compared with a binary measure like asthma. Likewise, more refined phenotyping will also improve the power to study gene-environment interactions.

Conclusion

GST genes have been considered asthma linked genes because of their intrinsic antioxidative mechanisms, but there is little evidence of an independent relationship with risk of asthma. However, there is more evidence for *GST* gene-environment interactions on asthma risk. The current evidence, although inconsistent, implicates oxidative stress pathways in the pathogenesis of asthma. These inconsistencies may be related to several factors including lack of use of refined asthma phenotypes and, or endotypes, and lack of consideration of gene haplotypes and gene-gene interactions. Our review explains only part of the complex interaction network of environmental exposures, antioxidant genes and asthma risk. Further larger studies and reviews on the interaction between toxic environmental exposures and antioxidant genes (taking multiple risk variants into account) are required to move toward a more precise asthma endotype approach.

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Data Transparency All data and materials support published claims and comply with field standards.

Author Contribution Dr. Dai, Dr. Lodge, and Dr. Bui all contributed to the study conception and design. Dr. Dai led the analysis and interpretation of data, with the support from Dr. Lodge and Dr. Bui. Dr. Dai wrote the initial draft of the manuscript which was critically revised for important content by all the authors. All authors approved the final version.

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Declarations

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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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