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An Exploratory Case-Only Analysis of Gene-Hazardous Air Pollutant Interactions and the Risk of Childhood Medulloblastoma

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Abstract

Background—There is evidence that exposure to chlorinated solvents may be associated with childhood medulloblastoma and primitive neuroectodermal tumor (M/PNET) risk. Animal models suggest genes related to detoxification and DNA repair are important in the carcinogenicity of these pollutants, however, there have been no human studies assessing the modifying effects of these genotypes on the association between chlorinated solvents and childhood M/PNET risk.

Procedure—We conducted a case-only study to evaluate census tract-level exposure to chlorinated solvents and the risk of childhood M/PNET in the context of detoxification and DNA repair genotypes. Cases ($n = 98$) were obtained from Texas Children's Hospital and MD Anderson Cancer Center. Key genotypes ($n = 22$) were selected from the Illumina Human 1M Quad SNP Chip. Exposure to chlorinated solvents (methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride) was estimated from the U.S. EPA's 1999 Assessment System for Population Exposure Nationwide (ASPEN). Logistic regression was used to estimate the case-only odds ratios and 95% confidence intervals (CIs).

Results—There were 11 significant gene-environment interactions associated with childhood M/PNET risk. However, after correcting for multiple comparisons, only the interaction between high trichloroethylene levels and *OGG1* rs293795 significantly increased the risk of childhood M/PNET risk (OR = 9.24, 95% CI: 2.24, 38.24, $Q = 0.04$).

Conclusions—This study provides an initial assessment of the interaction between ambient levels of chlorinated solvents and potentially relevant genotypes on childhood M/PNET risk. Our results are exploratory and must be validated in animal models, as well as additional human studies.

Keywords

Hazardous air pollutants; chlorinated solvents; DNA repair genes; detoxification genes; childhood medulloblastoma and primitive neuroectodermal tumor

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INTRODUCTION

Central nervous system (CNS) tumors are the second most common pediatric malignancy and the most common solid tumor in children [1]. Medulloblastoma and primitive neuroectodermal tumor (M/PNET) account for approximately 24% of childhood CNS tumor cases and have an overall incidence rate of 6.6 per 1,000,000 person-years [1]. Although 5-year survival has improved in recent years, the long-term consequences of treatment are significant [2]. In spite of the clinical importance of M/PNET, the etiology of these conditions remains unclear. Therefore, it is critical to identify modifiable risk factors in order to lessen the impact of M/PNET. Although environmental toxicants have been associated with the development of M/PNET [3]; much work remains to fully elucidate the relationship between specific groups of toxicants and M/PNET risk, including the assessment of gene-environment interactions.

The U.S. Clean Air Act of 1990 identified 189 environmental toxicants as hazardous air pollutants (HAPs). These pollutants are particularly important because: 1) they are known or suspected to cause a range of adverse health outcomes, including cancer [4]; 2) their levels are increasing in communities throughout the U.S. [5]; and 3) there are currently no national air quality standards for HAPs, as there are for the “criteria” air pollutants (e.g., carbon monoxide and ozone) as defined by the U.S. Environmental Protection Agency (EPA) [6]. Although HAPs are considered to have important health consequences, population-scale individual-level measurements of HAPs are nonexistent and monitoring of HAPs in communities throughout the U.S. is very limited. Consequently, the U.S. Environmental Protection Agency (EPA) has developed the Assessment System for Population Exposure Nationwide, or ASPEN model, to estimate annual concentrations of HAPs at the census tract level [7]. Independent assessments, including our own study in Texas [8], have concluded that estimates of selected HAPs obtained using the ASPEN model are a good surrogate for exposure measures based on personal and outdoor monitoring [9].

HAPs are a heterogeneous grouping of toxicants including chlorinated solvents (e.g., vinyl chloride), aromatic solvents (e.g., benzene), and heavy metals (e.g., cadmium). Among these pollutants, there is limited and equivocal evidence that chlorinated solvents are associated with adult [10, 11] and childhood brain tumors [3, 12, 13]. Chlorinated solvents are a family of chemical compounds that are commonly used in many industrial settings. Their uses include paint stripping (methylene chloride), dry cleaning (perchloroethylene), metal degreasing (trichloroethylene), and the production of polyvinyl chloride (vinyl chloride). The principal route of environmental exposure is inhalation of ambient air [14–16]. Many of these compounds have been identified as known (e.g., vinyl chloride), probable (trichloroethylene, perchloroethylene) or possible (methylene chloride) human carcinogens by the International Agency for Research on Cancer (IARC) [14–16].

The suspected mechanism of carcinogenicity for several chlorinated solvents (e.g., trichloroethylene) follows a well-established paradigm [17]. After exposure, these toxicants are either excreted or bioactived by Phase I and/or Phase II detoxification enzymes. Phase I reactions generally involve the introduction of a functional group, whereas Phase II reactions involve direct conjugation [18]. If xenobiotics, such as chlorinated solvents, are bioactivated by Phase I or Phase II enzymes, the reactive intermediates can form DNA adducts leading to strand breaks and other cytotoxic effects [17]. Because of this, studies assessing environmental exposure to these and similar toxicants should also account for genotypes related to detoxification of these exposures and DNA repair capacity (particularly base excision repair and nucleotide excision repair). Therefore, we conducted an exploratory study to evaluate exposure to environmental levels of chlorinated solvents and the risk of

childhood M/PNET in the context of detoxification and DNA repair genotypes using a case-only approach.

MATERIALS AND METHODS

Study subjects

The study population included 98 incident M/PNET cases recruited consecutively from Childhood Cancer Epidemiology and Prevention Center at Texas Children's Hospital (Houston, TX) between 1986 and 2010. Cases were <18 years of age and histopathologically confirmed (ICD-O-3 codes 9470–9474). After written informed consent was obtained from the parent, we obtained a blood sample from each participant. These samples were used to obtain DNA for genotyping. Demographic and clinical data were abstracted from medical records. Only cases who were residing in the state of Texas at the time of diagnosis were included based on the exposure assessment. The study protocol was approved by the Baylor College of Medicine and MD Anderson Cancer Center Institutional Review Boards.

Environmental Exposure Assessment

Based on previous studies of brain tumors [14–16], as well as ambient levels in Texas [5, 8], we selected the following chlorinated solvents for analysis: methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride. Census tract-based estimates of ambient levels of the selected chlorinated solvents were obtained from the U.S. EPA's 1999 ASPEN model [7, 19, 20]. The methods used for ASPEN have been described fully elsewhere [7, 20]. Briefly, ASPEN is part of the National Air Toxic Assessment (NATA) and is based on the EPA's Industrial Source Complex Long Term Model. It takes into account emissions data; rate, location, and height of pollutant release; meteorological conditions; and the reactive decay, deposition, and transformation of pollutants. ASPEN model results were first generated for 1990 as part of the U.S. EPA Cumulative Exposure Project and then again for 1996, 1999, and 2002 as part of NATA. We opted to use the 1999 modeled estimates as the U.S. EPA advises against using multiple assessments (e.g., 1999 + 2002). This is due to differences in the methodology of successive assessments [21]. Additionally, 1999 is an approximate midpoint within our study period (1986–2010). Ambient air levels of chlorinated solvents (and other HAPs) are reported as annual concentrations in $\mu g/m^3$ [20].

Residential air levels of the chlorinated solvents were estimated based on address at diagnosis as reported in medical records. Specifically, case addresses were mapped to their respective census tracts. This information was then linked to ASPEN census tract-level estimates of ambient levels of methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride.

Genotyping and SNP selection

Genotyping was performed using the Illumina Human 1M Quad SNP Chip according to manufacturer's instructions (Illumina, San Diego, USA). Samples were excluded when fewer than 95% of genotypes were called overall. For quality assurance purposes, duplicate samples were genotyped in the same batches.

As we were interested in genetic modifiers of environmental exposure to chlorinated solvents, we compiled a list of the fifteen key detoxification and DNA repair genes (base excision repair and nucleotide excision repair) suspected in toxicant-induced carcinogenesis [14–16, 22]. These genes and the corresponding number of SNPs available on the Illumina Human 1M Quad SNP Chip are listed in Table I. From this list of candidate SNPs (n = 348), those with a minor allele frequency <10% (n = 226) were eliminated from the analysis.

From the remaining 122 SNPs, tagSNPs with high linkage disequilibrium (r^2 >0.8) were identified for each gene [23]. TagSNPs (n = 22) were selected for analysis (Figure 1) using the SNPStats program [24]. As population stratification may bias case-only studies [25], we also included an additional 212 ancestry informative markers to account for population structure [26].

Statistical Analysis

Frequency distributions, means and standard deviations were determined for demographic and clinical variables among the case subjects. The means and standard deviations, as well as the 10th, 50th, and 90th percentiles for levels of methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride were compared between case census tracts and the state of Texas as a whole. Correlations between levels of methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride were determined using Spearman's rank correlation.

A case-only design was used to examine the interaction between exposure to ambient levels of selected chlorinated solvents and tagSNPs in detoxification and DNA repair genes (i.e., gene-environment interactions). In a case-only design, the entire sample consists of those with disease (i.e., cases) [27]. Specifically, M/PNET subjects were used to assess the association between the environmental exposure and the genotype. Details of the case-only design have been presented previously [27–29], and the design has been used extensively to evaluate gene-environment interactions (e.g., [30]) as it offers better precision than traditional case-control approaches [28]. Briefly, the case-only odds ratio (COR) is the odds of an environmental exposure (E) given the presence of a genetic factor (G) divided by the odds of E given the absence of G. The COR is reversible [29], such that it is also the odds of G given the presence of E divided by the odds of G given the absence of E. Therefore, the COR is interpreted as the multiplicative interaction between G and E in causing diease [29]. An important assumption is that of independence between E and G in the general population [28]. Schmidt and Schaid demonstrated that when there is independence between the E and G in the general population, the COR is equivalent to the interaction estimation based on risk ratios in a given source population [31]. For this study assessing the association between air pollutant exposure and selected genotypes, we believed this assumption was reasonable [25].

We conducted an unconditional logistic regression to estimate the case-only ORs and 95% confidence intervals (CIs) for assessing the interaction between each chlorinated solvent and genotype on childhood M/PNET risk. We classified the genotypes for each SNP based on the number of minor alleles (i.e., 0, 1, or 2), and categorized exposure as high versus low based on the 90th percentile of the distribution of each pollutant separately. In other words, low exposure (reference) was the <90th percentile, whereas high exposure was ≥90th percentile. We did this based on the assumption that more extreme levels would be associated with higher risk [32]. In the unconditional logistic regression models, the exposure variable was the dependent variable and the genotype was the independent variable. We used Structure version 2.3.3 [33] to determine the percent ancestry from each of three ancestry subgroups (African, Amerindian, and European) among the case population [33, 34]. This information was utilized in the unconditional logistic regression models (as a continuous variable for each subgroup) to account for potential population stratification [25]. The logistic model expression for our analysis is presented in the following equation, where E is the environmental factor, G is the genetic factor, and C is the covariate for ancestry:

$$\text{log odds (E)}=\beta_0+\beta_1(\text{G})+\beta_2(\text{C})$$

Because there were 88 pairwise interactions (four pollutants by 22 genotypes) examined in this study, the Benjamini and Hockberg method (false discovery rate) was used to calculate corrected *P*-value (i.e., *Q*-value) for the purpose of determining statistical significance [35]. We used Intercooled Stata, version 10.1 (StataCorp LP, College Station, TX) to conduct the statistical analyses.

RESULTS

Of the M/PNET cases, 60% had a diagnosis of medulloblastoma ($n = 59$), whereas 40% had a PNET diagnosis ($n = 39$) (Table II). The majority of the cases were male (71%, $n = 70$) and the mean age at diagnosis was 7.2 years. Among M/PNET cases, 46% ($n = 45$) were non-Hispanic White, 14% were non-Hispanic Black ($n = 14$), 36% were Hispanic ($n = 35$), and 4% reported another race/ethnicity ($n = 4$).

Based on the 1999 U.S. EPA ASPEN Model, the annual estimated mean and median levels of methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride were higher in case census tracts compared to all Texas census tracts (Table III). The 90th percentile of levels was slightly higher among case census tracts compared to all Texas census tracts for methylene chloride (0.76 μg/m^3 versus 0.75 μg/m^3), trichloroethylene (0.13 μg/m^3 versus 0.12 μg/m^3), and vinyl chloride (0.13 μg/m^3 versus 0.10 μg/m^3).

Levels of methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride were significantly correlated with one another ($P < 0.001$) (Table IV). However, some correlations were stronger (e.g. methylene chloride-trichloroethylene, $\rho = 0.93$) than others (perchloroethylene-vinyl chloride, $\rho = 0.43$). These correlations were not consistent across census tracts. For instance, the correlation between methylene chloride and trichloroethylene was not significant in those census tracts with the highest (i.e., ≥90th percentile) trichloroethylene levels ($\rho = 0.36$, $P = 0.30$).

Selected gene-environment interactions are presented in Table V. There were 11 significant interactions involving each of the chlorinated solvents (methylene chloride, $n = 3$; perchloroethylene, $n = 1$; trichloroethylene, $n = 3$; vinyl chloride, $n = 4$). However, after correcting for multiple comparisons, only one interaction remained statistically significant. Specifically, the case-only OR for those residing in census tracts with the highest estimated trichloroethylene levels (i.e., ≥90th percentile) and had the minor allele of *OGG1* rs293795 was statistically significant (OR = 9.24, 95% CI: 2.24, 38.24, $Q = 0.04$). Additionally, two interactions had borderline significance (i.e., $Q < 0.10$). M/PNET cases who resided in census tracts with the highest estimated trichloroethylene levels and the minor allele of *OGG1* rs159150 had an increased risk (OR = 6.50, 95% CI: 1.70, 24.81, $Q = 0.07$), whereas the minor allele of *NAT1* rs13253389 was protective among those living in census tracts with the highest estimated vinyl chloride levels (OR = 0.05, 95% CI: 0.01, 0.39, $Q = 0.09$).

DISCUSSION

We found a significant gene-environment interaction between *OGG1* rs293795 and exposure to ambient levels of the chlorinated solvent trichloroethylene, as estimated from the 1999 U.S. EPA ASPEN model, on the risk of childhood M/PNET. This association was seen in a relatively small study population after adjusting for population stratification and multiple comparisons. Interactions between trichloroethylene and other DNA repair gene SNPs were also observed, as well as interactions involving methylene chloride, perchloroethylene, vinyl chloride, and various detoxification and DNA repair genes on the risk of childhood M/PNET, however, these associations did not remain significant after correcting for multiple comparisons.

Trichloroethylene is a volatile compound used primarily for metal degreasing. The largest source is from industrial facilities and waste sites, and environmental exposure is most likely to occur via ambient air [36]. Trichloroethylene attains high concentrations (compared to blood) in the brain, which appears to be an important organ of toxicity [14]. Furthermore, IARC has identified trichloroethylene as a probable human carcinogen [14]. According to a recent risk assessment conducted in Southeast Texas using the U.S. EPA provisional inhalation unit risk estimate for trichloroethylene (1.7×10^{-6} μg/m^3) [37], ambient levels found in the census tracts with high exposure (i.e., ≥0.13 μg/m^3 in this study population) would be defined as having a possible cancer risk [5].

The *OGG1* gene encodes 8-oxoguanine glycosylase, which is involved in base excision repair. Specifically, the OGG1 enzyme is responsible for the excision of 8-oxoguanine, a mutagenic base byproduct, which is the result of exposure to reactive oxygen [38]. To our knowledge, *OGG1* genotypes have not been assessed previously in epidemiologic studies of trichloroethylene exposure. However, trichloroethylene and its metabolites have been shown to result in the formation of reactive oxygen species [39], which lead to the formation of 8-oxoguanine–DNA adducts and corresponding cytotoxic effects [38, 39]. Therefore, it is possible that trichloroethylene exposure is modified by *OGG1* genotypes. *OGG1* rs293795 is an intronic (non-coding) SNP and is not in a repeat region [40]. Although *OGG1* rs293795 has not been implicated in childhood brain tumor risk, this SNP does appear to be associated with several other tumors including breast [41] and prostate cancer [42]. As in our study, the minor allele of *OGG1* rs293795 (A>G) conferred risk for both breast and prostate cancer.

There is limited epidemiologic evidence for the association between trichloroethylene exposure and childhood M/PNET risk. Some parental occupational studies have indicated an association between solvent exposure and childhood brain tumor risk [13, 43]. For instance, fathers employed in motor vehicle-related occupations, where exposure to trichloroethylene is possible, were at a greater risk of having children with PNET (OR = 2.70, 95% CI: 1.11, 6.60) [44]. Additionally, mothers employed in professions where solvent exposure is likely to occur (electronic parts and components manufacturing; textile and garment workers) were at a greater risk of having children with brain tumors (OR = 13.78, 95% CI: 1.47, 129.05 and OR = 7.25, 95% CI: 1.42, 37.03; respectively) [43]. Whereas other parental occupational studies have found little evidence of an association between solvent exposure and childhood brain tumor risk (reviewed in [45]). There have been a few studies assessing environmental exposures to solvents and M/PNET risk. In one study assessing parental hobbies, there was suggestive evidence of an association between solvent-related exposures and M/PNET risk (OR = 1.4, 95% CI: 0.8, 2.6) [3]. Equivocal findings in previous studies of trichloroethylene (and other solvent exposures) and M/PNET risk may be due to differences in exposure assessment, when exposure was assessed (e.g., during pregnancy or at diagnosis), heterogeneous and small case groups, as well as not accounting for genotypes relevant to the metabolism of these toxicants.

The two major limitations of this study are the small sample size (98 cases) and the single ecological assessment of chlorinated solvents based on 1999 ASPEN estimates. Due to the small sample size, this was primarily an exploratory analysis in which we were only able to detect strong effects. However, we did identify a significant interaction (even after adjusting for multiple comparisons) and potential candidate gene-environment interactions for investigation in larger studies of childhood M/PNET (a relatively rare condition). Regarding the exposure assessment, ASPEN data were not available for the entire study period; therefore we used 1999 as a surrogate for other years. Although this may result in exposure misclassification as levels are likely to change over time, we used a relative ranking of exposure (i.e., high versus low), therefore census tracts with high levels of chlorinated

solvents in one year are likely to remain in the "high" category relative to census tracts with lower levels as the sources of chlorinated solvents (e.g., industrial facilities and waste sites) were unlikely to change during the study period [5, 19]. Furthermore, as there are no other sources of population-scale individual-level measurements of HAPs, ASPEN provides a cost-effective and exploratory method for evaluating the association between HAPs and adverse outcomes. Therefore, the ASPEN model has been used in previous studies of childhood cancer [46], birth defects [32], and autism [47], even when only one year of ASPEN data is available across multiple study years.

A second issue related to the exposure assessment is the use of address at diagnosis. This could introduce exposure misclassification if there is a great deal of residential mobility between the critical window of exposure and diagnosis. There have been no assessments of the impact of residential mobility on exposure assignment for childhood M/PNET. However, our own research on the impact of residential mobility during pregnancy (i.e., the period between preconception and delivery) indicated that maternal residential movement in Texas is generally within short distances, is typically not different between cases and controls, and does not significantly influence exposure assessment using ASPEN data [48]. Additionally, a study in California suggested changes in residence between delivery and diagnosis did not change urban/rural status for most children (>80%) with leukemia [49], an important predictor of exposure to HAPs [5, 8, 9, 48].

Another limitation is the inability to tease apart the effects of multiple chlorinated solvents on disease risk. This is especially true since levels of methylene chloride, perchloroethylene, trichloroethylene, and vinyl chloride were significantly correlated with one another across all census tracts. However, these correlations were not as strong in census tracts with the highest exposure level. For instance, levels of trichloroethylene were neither strongly nor significantly associated with levels of methylene chloride ($\rho = 0.36$, $P = 0.30$), perchloroethylene ($\rho = 0.04$, $P = 0.92$), or vinyl chloride ($\rho = 0.40$, $P = 0.26$) in census tracts where trichloroethylene levels were $\geq 90^{th}$ percentile. Therefore, our results for trichloroethylene at the highest exposure level do appear to be distinct from any potential confounding effects by the other related chlorinated solvents.

A general limitation to this and other case-only studies is the inability to evaluate the independent effects of the exposures or genotypes in question [27]. However, we selected exposures and genotypes based on previously reported associations [36, 45]. Another limitation with the case-only design involves the assumption of independence between the environmental exposure and genotype in the general population [28]. As stated, for these and similar exposures (e.g., air pollution), we believed this assumption was reasonable [25].

Strengths of this study include a well-characterized population of M/PNET cases. We were also able to account for genotypes related to the metabolism of chlorinated solvents [38]. Furthermore, we used a tagSNP approach in order to reduce the potential number of comparisons [23]. Finally, as recent evidence suggests case-only studies are subject to the same concerns related to population stratification as case-control studies [25], we used 212 ancestry informative markers to account for population structure [26].

This study provides an initial assessment of the interaction between ambient levels of chlorinated solvents and potentially relevant genotypes on childhood M/PNET risk. Our analyses suggest an interaction between ambient levels of trichloroethylene and *OGG1* rs293795 is associated with the risk of childhood M/PNET. We believe future investigations should include additional measures of exposure (e.g., air pollutant monitoring and biomarker data), larger sample sizes to determine moderate and modest interactions, as well as the inclusion of additional pollutants (e.g., heavy metals) and genotypes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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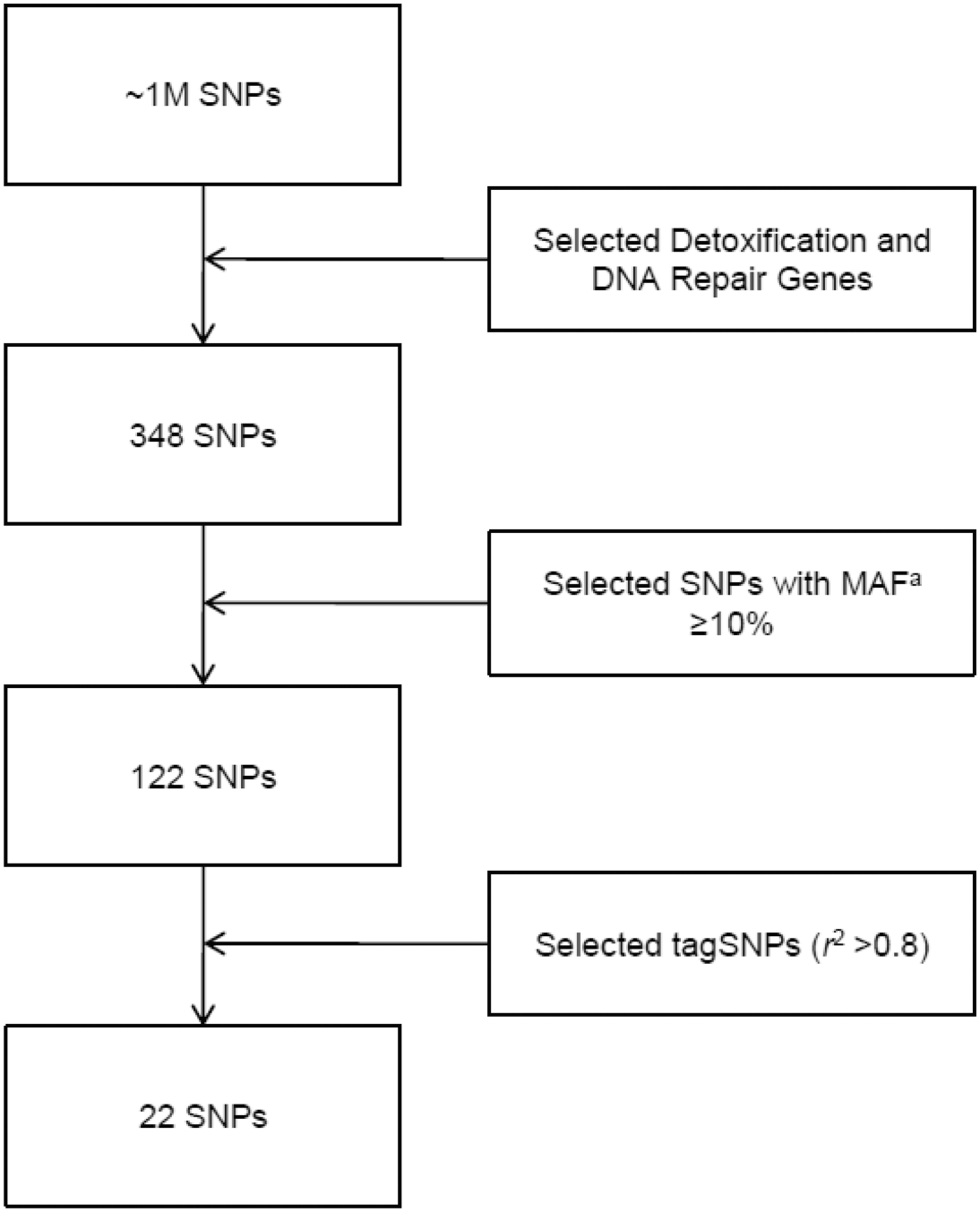

Figure 1.
Detoxification and DNA Repair SNP Selection Process.
[a] Minor Allele Frequency

Table I

Candidate Detoxification and DNA Repair Genes

Pathway	Gene Symbol	No. of SNPs[a]
Phase I Detoxification	*CYP1A1*	12
	CYP1A2	14
	CYP1B1	29
	CYP2E1	43
Phase II Detoxification	*EPHX1*	26
	GSTA4	41
	GSTM1	5
	GSTM3	12
	GSTP1	16
	NAT1	75
	NAT2	24
DNA Repair		
Base Excision Repair	*OGG1*	11
	XRCC1	21
Nucleotide Excision Repair	*ERCC1*	12
	XPA	7

[a]Based on the Illumina Human 1M Quad SNP Chip

Table II

Characteristics of Childhood Medulloblastoma and Primitive Neuroectodermal Tumor Cases

Characteristic	Childhood M/PNET[a] Cases (*N* = 98)
Sex, no. (%)	
Male	70 (71.4)
Female	28 (28.6)
Age at Diagnosis (years), mean (SD)	7.2 (4.8)
Race/ethnicity, no. (%)	
Non-Hispanic White	45 (45.9)
Non-Hispanic Black	14 (14.3)
Hispanic	35 (35.7)
Other	4 (4.1)
Histology, no. (%)	
Medulloblastoma	59 (60.2)
PNET	39 (39.8)

[a]Medulloblastoma and primitive neuroectodermal tumor

Table III

Characteristics of Methylene Chloride, Perchloroethylene, Trichloroethylene, and Vinyl Chloride levels (in μg/m^3) from the 1999 U.S. EPA ASPEN Model among M/PNET Case and Texas Census Tracts

Pollutant	Cases					Texas				
	Mean	SD	10th	50th	90th	Mean	SD	10th	50th	90th
Methylene Chloride	0.49	0.24	0.09	0.51	0.76	0.44	0.29	0.09	0.43	0.75
Perchloroethylene	0.21	0.12	0.02	0.22	0.33	0.18	0.14	0.01	0.17	0.33
Trichloroethylene	0.09	0.07	0.05	0.09	0.13	0.08	0.03	0.05	0.08	0.12
Vinyl Chloride	0.08	0.07	0.0003	0.08	0.13	0.06	0.04	0.00006	0.06	0.10

Table IV

Correlations Between Methylene Chloride, Perchloroethylene, Trichloroethylene, and Vinyl Chloride from the 1999 U.S. EPA ASPEN Model for Texas Census Tracts

	Methylene Chloride	Perchloroethylene	Trichloroethylene	Vinyl Chloride
Methylene Chloride	1.00			
Perchloroethylene	0.89	1.00		
Trichloroethylene	0.93	0.78	1.00	
Vinyl Chloride	0.57	0.43	0.57	1.00

$P < 0.001$

Table V

Significant Gene-Environment Interactions Associated with Childhood M/PNET

Pollutant	Gene	RefSNP	OR[a]	95% CI	*P*-value	*Q*-value[b]
Methylene chloride	*OGG1*	rs293795	4.48	1.35, 14.87	0.01	0.17
	NAT2	rs4271002	4.88	1.36, 17.58	0.02	0.17
	GSTM3	rs7483	2.93	1.06, 8.06	0.03	0.28
Perchloroethylene	*NAT2*	rs4271002	4.40	1.22, 15.91	0.02	0.23
Trichloroethylene	*OGG1*	rs293795	9.24	2.24, 38.24	0.002	0.04
	OGG1	rs159150	6.50	1.70, 24.81	0.006	0.07
	ERCC1	rs1007616	0.19	0.05, 0.78	0.02	0.16
Vinyl chloride	*NAT1*	rs13253389	0.05	0.01, 0.39	0.004	0.09
	CYP1B1	rs1800440	4.15	1.17, 14.67	0.03	0.27
	EPHX1	rs1051740	0.17	0.03, 0.95	0.04	0.27
	ERCC1	rs1007616	0.29	0.08, 0.99	0.04	0.27

Abbreviations: CI, confidence interval; OR, odds ratio;

[a]Adjusted for population stratification using ancestry informative markers;

[b]*P*-value corrected for multiple comparisons using false discovery rate