

Nicotine Metabolizing Genes *GSTT1* and *CYP1A1* in Sudden Infant Death Syndrome

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Received 10 February 2006; Accepted 6 April 2006

Exposure to tobacco, both to the developing fetus as well as in the postnatal period, has been identified as a key risk factor in the etiology of sudden infant death syndrome (SIDS). Polymorphisms in both the *GSTT1* and *CYP1A1* genes have been reported to impact the metabolic detoxification process for cigarette smoke and have been associated with low birth weight. Thus, expression of polymorphisms in these genes may account for the varying susceptibility to the adverse health consequences of tobacco exposure, including SIDS. We hypothesized that functional polymorphisms in *GSTT1* (gene deletion) and *CYP1A1* (m1, m2, and m3) might be associated with SIDS risk. DNA was prepared from 106 SIDS cases and 106 ethnicity- and gender-matched controls using standard methods. Regions of interest were amplified using PCR, subjected to enzyme digestion, and analyzed on agarose gel. No association was observed between the *GSTT1* gene deletion or the *CYP1A1*

m1, m2, and m3 polymorphisms with SIDS risk when considered independently or in combination. These results indicate that the *GSTT1* gene deletion and polymorphisms of *CYP1A1* are not responsible for increased SIDS risk in our dataset. However, because SIDS cases with confirmed history of nicotine exposure were limited (7/106 cases), a relationship that might be apparent in a cohort with a large subset of SIDS cases with known history of nicotine exposure cannot be ruled out. A prospective study of SIDS cases with nicotine exposure history is necessary to resolve the relationship between nicotine metabolizing genes and SIDS. © 2006 Wiley-Liss, Inc.

Key words: nicotine; autonomic nervous system; sudden infant death syndrome; glutathione S-transferase theta 1; cytochrome P-450 1A1

How to cite this article: Rand CM, Weese-Mayer DE, Maher BS, Zhou L, Marazita ML, Berry-Kravis EM. 2006. Nicotine metabolizing genes *GSTT1* and *CYP1A1* in sudden infant death syndrome. *Am J Med Genet Part A* 140A:1447–1452.

INTRODUCTION

While the etiology of sudden infant death syndrome (SIDS) remains unclear, recent studies have begun to indicate a genetic basis for the disease [Narita et al., 2001; Weese-Mayer et al., 2003a,b, 2004]. Because observations consistent with autonomic nervous system (ANS) dysregulation have been widely reported in conjunction with SIDS [Kelly et al., 1986; Schechtman et al., 1988; Kahn et al., 1992; Ponsonby et al., 1992; Meny et al., 1994; Franco et al., 1998, 1999; Ledwidge et al., 1998; Schwartz et al., 1998], early genetic studies have focused on genes pertinent to the regulation and development of the ANS. The serotonin transporter protein (*5-HTT*) gene, involved in ANS regulation, was the first

gene associated with SIDS risk. Two functional polymorphisms, located in the *5-HTT* promoter and in intron 2, and both resulting in enhanced

Grant sponsor: CJ Foundation for SIDS; Grant sponsor: Justin Carl Suth SIDS Research Fund; Grant sponsor: Joseph Tyler Gertler SIDS Research Fund; Grant sponsor: University of Maryland Brain & Tissue Bank for Developmental Disorders; Grant sponsor: Spastic Paralysis & Allied Diseases of the CNS Research Foundation of Illinois-Eastern Iowa District Kiwanis International.

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DOI 10.1002/ajmg.a.31306

transcription of *5-HTT*, were linked to the SIDS phenotype in Japanese, African-American, and Caucasian populations [Narita et al., 2001; Weese-Mayer et al., 2003a] and in African-American populations, respectively [Weese-Mayer et al., 2003b]. In other genes related to ANS development, 11 rare, protein-changing polymorphisms located in paired-like homeobox (*PHOX*) 2A, receptor tyrosine kinase (*RET*), endothelin converting enzyme-1 (*ECE1*), T-cell leukemia homeobox protein (*TLX3*), and engrailed-1 (*EN1*) genes were identified in 15.2% of SIDS cases compared to 2.2% of controls [Weese-Mayer et al., 2004]. Recently, a common single nucleotide polymorphism in intron 2 and a preponderance of coding region polymorphisms in exon 3 of *PHOX2B*, the disease-defining gene in congenital central hypoventilation syndrome (CCHS) [Weese-Mayer et al., 2005], were identified in SIDS cases [Rand et al., in press]. These results taken together strongly support a genetic basis for SIDS among genes involved in the embryologic origin and development of the ANS.

Exposure to tobacco, both prenatal as well as postnatal, has been identified as a key risk factor in the etiology of SIDS [Blair et al., 1996; Anderson and Cook, 1997; Brooke et al., 1997; MacDorman et al., 1997; Mitchell et al., 1997]. Additionally, tobacco exposure has been identified as an established teratogen to the developing fetus and has been linked to premature birth, placental abruption, intrauterine growth restriction, stillbirths, and spontaneous miscarriages [Kline et al., 1977; Naeye et al., 1977; Himmelberger et al., 1978; Shiono et al., 1986, 1995; Schwartz-Bickenbach et al., 1987; Raymond and Mills, 1993; Raymond et al., 1994; Gocze et al., 1999; Pollack et al., 2000; Wang et al., 2002]. A relationship between tobacco exposure and altered ANS function has long been recognized for adults with both chronic [Niedermaier et al., 1993; Piha, 1994; Kotamaki, 1995; Lucini et al., 1996] and acute [Pope et al., 2001] exposure and more recently for infants exposed to smoke prenatally [Franco et al., 2000]. Based on these relationships between SIDS, tobacco exposure, and ANS dysregulation, genes involved in nicotine metabolism were identified as possible candidate genes for further study of the genetic basis for SIDS.

The ability to convert toxic metabolites in cigarette smoke to less harmful compounds is key to minimizing the adverse health effects of exposure to tobacco. Polycyclic aromatic hydrocarbons (PAHs), some of the most important carcinogens in cigarette smoke, are metabolized through a two-stage process. In phase 1 inhaled PAHs are activated by converting the hydrophobic compounds into hydrophilic compounds which are reactive and have electrophilic intermediates capable of binding DNA. Cytochrome P-450 1A1 (*CYP1A1*) encodes aryl hydrocarbon hydroxylase, a major enzyme responsible for phase 1 metabolism of PAHs. During the second phase of the metabolism of PAHs detoxification occurs through enzymes such as glutathione S-transferases (*GSTs*) or uridine diphosphate (*UDP*)-glucuronosyltransferase through transformation into compounds that can be excreted from the body. *GSTT1* is encoded by the *GSTT1* gene, and is a major enzyme in phase 2 of cigarette smoke metabolism [Hayashi et al., 1992; Nakachi et al., 1993; Bartsch et al., 2000]. Polymorphisms in both the *CYP1A1* and *GSTT1* genes [Ishibe et al., 1997; Bartsch et al., 2000] have been reported to impact the metabolic detoxification process for cigarette smoke. Thus, expression of polymorphisms in these genes have been associated with low birth weight [Wang et al., 2002], and may account for the varying susceptibility to other adverse health consequences of cigarette smoke exposure, including SIDS. As such, we hypothesized that functional polymorphisms in the *GSTT1* and *CYP1A1* (m1, m2, and m3) genes (Table I) might be associated with SIDS in Caucasian and/or African-American cohorts.

MATERIALS AND METHODS

Study Population

Two distinct groups were investigated in this study: 106 SIDS cases and 106 control subjects matched for gender and ethnicity. A subset (92/106) of these SIDS cases and matched controls were included in previous publications [Weese-Mayer et al., 2003a,b, 2004]. Ethnicity was assigned based on self report or report of the mother. This study was approved by the

TABLE I. Genotyping of *GSTT1* and *CYP1A1* Variants

Gene	Mutation	Primers (Location)	Restriction enzyme	Genotype	Cut position	Fragment length ^a
<i>GSTT1</i>	Gene deletion	GSTF/GSTR	None	Wild-type (no deletion)	None	480
				Mutation (deletion)	None	None
<i>CYP1A1</i>	m1; 6235 T → C	M3F/P80	Msp1	Wild-type (T)	None	899
				Mutation (C)	6,234	693, 206
	m2; 4889 A → G	M2F/M2R	BsrD1	Wild-type (A)	4,887	149, 55
				Mutation (G)	None	204
	m3; 5639 T → C	M3F/P80	Msp1	Wild-type (T)	None	899
				Mutation (C)	5,638	802, 97

^aCorresponds to band sizes seen on gel, given in base pairs.

Rush University Medical Center and the University of Pittsburgh institutional review boards.

SIDS cases. One hundred six SIDS cases (mean age at death 95 days \pm 52; median age 85 days, 25th and 75th percentiles: 56 and 111 days, respectively) with a diagnosis made by the University of Maryland Medical Examiner were identified in the University of Maryland Brain and Tissue Bank (24 African-American females, 29 African-American males, 19 Caucasian females, and 34 Caucasian males). The diagnosis of SIDS was based on the accepted definition: the sudden and unexpected death of an infant less than 1 year of age which remains unexplained after a thorough clinical history, death scene investigation, and post-mortem examination [Willinger et al., 1991]. A questionnaire assessment of prenatal and postnatal tobacco exposure in the 106 SIDS cases indicated confirmed exposure in 7/106 cases (personal communication H.R. Zielke), precluding statistical analysis by exposure.

Control subjects. One hundred six unrelated living control subjects were matched for ethnicity and gender to the SIDS cases with a 1:1 match ratio. After informed consent was obtained, a three-generation family history was taken for each control to ensure that no family member had a diagnosis of SIDS, Hirschsprung disease, CCHS, apparent life threatening event, primary (non-acquired) disorder of ANS dysregulation, or tumor of neural crest origin.

DNA Preparation

Frozen frontal cortex brain tissue from SIDS subjects was obtained from the University of Maryland Brain and Tissue Bank for Developmental Disorders (<http://medschool.umaryland.edu/btbank/main.html>). Blood from control subjects (3–10 cc) was obtained by venipuncture and collected in an EDTA tube. Genomic DNA was isolated from the brain and blood samples utilizing standard methods [Weese-Mayer et al., 2003a].

Polymerase Chain Reaction and Genotyping Procedure

Glutathione S-transferase theta 1 (GSTT1). *GSTT1* was amplified using primer pairs 5'-TTC CTTACTGGTCCTCACATCTC-3' (forward) and 5'-TC ACCGGATCATGGCCAGCA-3' (reverse) as described previously [Pemble et al., 1994]. A 204 base-pair product of the *CYP1A1* gene was coamplified with *GSTT1* as a control to ensure adequacy of the DNA and PCR reaction, using primer pairs M2F and M2R (sequence below). PCR products were visualized on 1% agarose gels stained with ethidium bromide. The presence of the amplified 480 base-pair product indicated presence of the *GSTT1* gene while absence of a 480 base-pair product indicated a homozygous *GSTT1* deletion.

Cytochrome P-450 1A1 (CYP1A1). *CYP1A1* was amplified using primer pairs M3F 5'-GGCTGAG-CAATCTGACCCTA-3' (forward) and P80 5'-TAG-GAGTCTTGTCTCATGCCT-3' (reverse) for m1 and m3 determination and M2F 5'-CTGTCTCCCTCTGGT TACAGGAAGC-3' (forward) and M2R 5'-TTCCACCC GTTGACAGCAGGATAGCC-3' (reverse) for m2 determination as previously described [Cascorbi et al., 1996]. PCR products were digested with restriction enzymes (Table I) to generate fragments and visualized on 2% agarose gels stained with ethidium bromide. Genotypes were determined from band sizes as shown in Table I.

Statistics

For each case-control comparison we computed standard Chi-square tests of independence between genotype or allele frequency and phenotype. Under the null hypothesis of no genotype or allele frequency differences, the test statistic has a χ^2 distribution with degrees of freedom equal to one less than the number of alleles or genotypes. We also performed χ^2 tests of Hardy Weinberg Equilibrium for each of the *CYP1A1* marker genotype distributions in the control population. To address the issue of a sparse contingency table for *CYP1A1*, Monte Carlo tests of association as implemented in computer algorithm CLUMP were used [Sham and Curtis, 1995].

RESULTS

GSTT1

The frequency of the *GSTT1* homozygous deletion genotype did not differ between SIDS cases (22/106; 20%) and matched controls (32/106; 30%) in either the complete sample ($P=0.12$) or the Caucasian or African-American subgroups ($P=0.16$ and $P=0.39$, respectively; Table II).

CYP1A1

No association with SIDS was observed when the genotype distribution was considered at the *CYP1A1* m1 polymorphism ($P=0.38$), the *CYP1A1* m2 polymorphism ($P=0.17$), or the *CYP1A1* m3 polymorphism ($P=0.70$; Table II). Allele frequency comparisons were conducted for the *CYP1A1* m1 and m2 polymorphisms. No association was observed in either comparison, although a trend toward association was observed ($P=0.07$) with SIDS cases containing the m2 rare allele (G) more frequently than controls. The markers *CYP1A1* m1 ($\chi^2=1.601$, $P=0.21$) and *CYP1A1* m3 ($\chi^2=0.068$, $P=0.80$) were in Hardy Weinberg equilibrium in the control group but there was significant evidence that *CYP1A1* m2 ($\chi^2=10.44$, $P=0.001$) was not.

TABLE II. Comparisons of Genotype Frequency Distributions for *GSTT1* and *CYP1A1* m1, m2, and m3 in SIDS Cases and Matched Controls

	<i>GSTT1</i> ^a						<i>CYP1A1</i> m1 ^b						<i>CYP1A1</i> m2 ^b						<i>CYP1A1</i> m3 ^b																									
	SIDS			Control			SIDS			Control			SIDS			Control			SIDS			Control																						
	Present	Deleted	<i>P</i> value	TT	TC	CC	TT	TC	CC	AA	AG	GG	AA	AG	GG	AA	AG	GG	TT	TC	TC	TT	TC	TC																				
A.A. ^c	0.75	0.25	0.39	0.51	0.43	0.06	0.65	0.27	0.08	0.27	0.08	0.02	0.94	0.06	0.00	0.23	0.92	0.08	0.90	0.10	0.70	0.83	0.17	0.28	0.16	0.59	0.87	0.13	0.00	0.96	0.02	0.02	0.26	1.00	0.00	1.00	1.00							
Cauc. ^c	0.79	0.21	0.12	0.63	0.34	0.03	0.70	0.25	0.05	0.38	0.88	0.11	0.01	0.95	0.04	0.01	0.17	0.96	0.04	0.95	0.05	0.70	0.79	0.21	0.30	0.63	0.34	0.03	0.70	0.25	0.05	0.38	0.88	0.11	0.01	0.95	0.04	0.01	0.17	0.96	0.04	0.95	0.05	0.70

^a*GSTT1* comparisons are the wild-type and heterozygous genotypes (present) compared to the homozygous deleted genotype.
^bIn the *CYP1A1* m1, m2, and m3 comparisons the wild-type genotype is listed first followed by the heterozygous genotype and, where applicable, the homozygous rare allele genotype.
^cGenotype frequencies are based on 106 SIDS cases (53 African-American (A.A.)/53 Caucasian (Cauc.)) and 106 gender- and ethnicity-matched controls.

Allele combinations. When multiple alleles were considered in combination, no association was found between cases containing one or more of the *CYP1A1* rare alleles (m1, m2, and/or m3) and the SIDS phenotype ($P=0.58$). Likewise no association was observed between cases containing both the *GSTT1* deletion genotype and a rare *CYP1A1* allele (m1, m2 and/or m3) with the SIDS phenotype ($P=0.85$).

Ethnic comparison. Higher frequencies of the variant allele (*GSTT1* and/or *CYP1A1*) combinations were observed in the African-American subgroups compared to Caucasian subgroups ($P=0.02$; Table II) likely due to the higher genetic heterogeneity in that population.

DISCUSSION

This study examined the relationship between the *GSTT1* deletion, the *CYP1A1* m1, m2, and m3 polymorphisms, and SIDS risk in a cohort of 106 African-American and Caucasian SIDS cases and matched controls. Based on the established relationships between SIDS, tobacco exposure, and ANS dysregulation, coupled with the impact of *GSTT1* and *CYP1A1* polymorphisms on nicotine metabolism [Ishibe et al., 1997; Bartsch et al., 2000], these genes were hypothesized to be candidates for further characterization of the genetic basis for SIDS. However, our analysis did not reveal an association between the *GSTT1* deletion or the *CYP1A1* polymorphisms (m1, m2, or m3) and SIDS risk either as separate risk factors or when considered in combination.

Tobacco exposure, both to the developing fetus and in the postnatal period, has been shown to be a leading modifiable risk factor for SIDS [Blair et al., 1996; Anderson and Cook, 1997; Brooke et al., 1997; MacDorman et al., 1997; Mitchell et al., 1997]. Genetic traits that alter the metabolic efficiency of, and thereby increase susceptibility to damage from, toxins encountered through tobacco exposure could serve as important risk factors for SIDS. Both the *GSTT1* and *CYP1A1* genes have been shown to be involved in the metabolism and detoxification of organic solvents, including those encountered through tobacco exposure, and have been shown to contain a gene deletion and several polymorphisms, respectively, functional in nicotine metabolism [Ishibe et al., 1997; Bartsch et al., 2000]. Wang et al. [2002] examined the relationship between maternal cigarette smoking and both birth weight and gestational age in relation to the *GSTT1* deletion and to one of the *CYP1A1* polymorphisms, m1. Both the reduction in birth weight and the shortened gestation period observed in infants born to mothers exposed to smoke during pregnancy was greater when either the *GSTT1* deletion or the *CYP1A1* m1

polymorphism was present and was greatest when both of these were found in conjunction. Additionally, the *GSTT1* deletion as well as the *CYP1A1* polymorphisms m1, m2, and m3 have been linked to lung cancer risk in light smokers [Kawajiri et al., 1990; Cascorbi et al., 1996; Xu et al., 1996; Ishibe et al., 1997], supporting an effect for each in tobacco toxin metabolism efficiency.

In this study, ethnic variation was observed with a prevalence of the *GSTT1* deletion and *CYP1A1* polymorphisms being found in African-American samples compared to Caucasian samples. This observation is interesting in light of the increased risk of SIDS in African-American populations compared to controls, although it is likely a non-specific reflection of the increased genetic variability in populations of African descent.

The limitations of this study must be recognized. Because of the nature of the NIH-funded tissue bank, no detailed history is provided regarding each SIDS case limiting access to phenotyping and other relevant demographic information. While we are very confident in the diagnosis of SIDS in the identified subjects because of the rigor provided by the medical examiner responsible for the bank, the sample size is limited as is the racial/ethnic representation, both factors that may impact our results. Further, there may be some unknown selection bias acting on the control group as the m2 allele is not in Hardy-Weinberg equilibrium across the genotypes in the control sample. The largest limitation of this study is the lack of definitive smoke exposure history for the subjects with SIDS. Assessment of prenatal and postnatal tobacco exposure was available in the SIDS cases, but denial or "no response" were the most prevalent answers despite an anticipated increase in rate of smoking exposure in SIDS. The SIDS cohort is expected to represent a combination of cases with exposure and without exposure, so the presence of the no exposure cases will be expected to limit significance. Thus, it is possible that the trend toward an association with the *GSTT1* deletion and the *CYP1A1* m2 allele would be significant in a larger group of cases or a group containing only those cases with cigarette smoke exposure.

An increased risk of SIDS has been observed in infants exposed to cigarette smoke. Variations of the *GSTT1* and *CYP1A1* genes, important in metabolism of tobacco toxins, do not seem to play a role in this heightened susceptibility in this study. The recognized relationship between tobacco exposure and SIDS risk indicates that examination of these and additional genes involved in tobacco metabolism in a prospective SIDS cohort known to have a history of confirmed smoke exposure may shed light on genetic factors that mediate the role that tobacco exposure plays in susceptibility to SIDS.

ACKNOWLEDGMENTS

We would like to thank the parents of the SIDS cases for their gracious tissue donations, the control subjects who shared their DNA, and Dr. H. Ronald Zielke, Director of the University of Maryland Brain and Tissue Bank for his recovery of available nicotine exposure data.

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