

Research Letter
Sudden Infant Death Syndrome:
Case-Control Frequency Differences in Paired
Like Homeobox (*PHOX*) 2B Gene

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To the Editor:

Although the etiology of Sudden Infant Death Syndrome (SIDS) remains unclear, recent studies have begun to uncover a genetic basis that may play a role independently or in combination with environmental cofactors. The serotonin transporter gene (*5HTT*, *SLC6A4*) was the first gene linked to SIDS. Narita et al. [2001] demonstrated an association between a promoter polymorphism in *5HTT*, known to differentially regulate transporter expression, and SIDS risk by describing an excess of the more effective promoter long (L) allele in the Japanese SIDS group relative to controls. We confirmed this association in Caucasian and African-American SIDS cases [Weese-Mayer et al., 2003a] and then reported an association between SIDS and a regulatory *5HTT* intron 2 polymorphism in African-American SIDS cases [Weese-Mayer et al., 2003c]. The intron 2 association also involved increased SIDS risk with the genotype leading to more effective transporter production (12 allele). Further, the promoter and intron 2 loci were in linkage disequilibrium, and the L-12 haplotype was significantly associated with SIDS in the African-American subgroups. These results provide evidence for a relationship between SIDS risk and *5HTT* activity and represented a first step in the study of a genetic basis for SIDS.

PHOX2B, a key gene in the development of central serotonergic (5HT) neurons, encodes a highly conserved homeobox domain transcription factor with two stable polyalanine repeats of 9 and 20

residues. Recent studies indicate that *PHOX2B* plays a regulatory role in the selection between motor neuron or serotonergic neuronal fate in the development of the central nervous system [Pattyn et al., 2003, 2004]. Loss of function experiments in mice have shown that for the transition from motor neuron production to 5HT neuron production to commence, downregulation of *PHOX2B* is required [Pattyn et al., 2003]. Further, Panigrahy et al. [2000] reported a decrease in serotonergic receptor binding in key medullary regions that contain serotonergic cell bodies in SIDS cases. These reports identify a role for *PHOX2B* in the development of the serotonin system and potentially a relationship between 5HT system development and *PHOX2B* in SIDS risk.

Studies investigating the pathophysiology of infants who succumbed to SIDS indicate an abnormality in the regulation of the autonomic nervous system (ANS) [Schechtman et al., 1988; Ponsonby

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et al., 1992; Franco et al., 1998, 1999; Schwartz et al., 1998]. We previously focused on genes pertinent to the embryological development of the ANS [Weese-Mayer et al., 2004], and identified 11 rare protein-changing polymorphisms in 15.2% of SIDS cases and 1 polymorphism in 2.2% of controls. The receptor tyrosine kinase (*RET*) gene accounted for five of the rare protein-changing polymorphisms in SIDS cases. These results represented the first report describing specific polymorphisms in genes involved in the embryologic origin of the ANS that may confer some risk for SIDS.

PHOX2B is the disease-defining gene in Congenital Central Hypoventilation Syndrome (CCHS) [Amiel et al., 2003; Sasaki et al., 2003; Weese-Mayer et al., 2003b; Matera et al., 2004; Trochet et al., 2005], a disease characterized by ANS dysregulation [Marazita et al., 2001]. *PHOX2B* is a key gene in ANS development with a role in early embryologic development as a transcriptional activator in promotion of pan-neuronal differentiation including upregulation of proneural genes, *MASH1* expression, and motoneuronal differentiation [Lo et al., 1998]. *PHOX2B* has a separate role by a different pathway wherein it represses expression of inhibitors of neurogenesis [Lo et al., 1999]. Further, *PHOX2B* is required to express tyrosine hydroxylase, dopamine beta hydroxylase [Hirsch et al., 1998], and *RET*, and to maintain *MASH1*, thereby regulating noradrenergic neuronal specification in vertebrates [Pattyn et al., 1999]. Finally, *PHOX2B* knock-out mice ($-/-$) do not survive as ANS circuits either fail to form or degenerate [Pattyn et al., 1999].

Based on the established relationship between SIDS, *5HTT*, and ANS dysregulation coupled with the recognized role of *PHOX2B* in ANS and serotonergic system development, we hypothesized that a subset of SIDS cases might have unique mutations or polymorphisms in *PHOX2B* and that these variations may interact with those previously identified in *5HTT* and *RET* to modify SIDS risk.

Two distinct groups were investigated in this study: 91 SIDS cases and 91 control subjects matched for gender and ethnicity, a subset (88/91) of which were included in previous publications [Weese-Mayer et al., 2003a,c, 2004]. SIDS cases (23 African-American males, 22 African-American females, 30 Caucasian males, and 16 Caucasian females) were identified in the University of Maryland Brain and

Tissue Bank (<http://medschool.umaryland.edu/btbank/main.html>). A diagnosis of SIDS was made by the University of Maryland Medical Examiner based on the accepted definition [Willinger et al., 1991]. A three-generation family history was taken for each control to ensure absence of SIDS, Hirschsprung Disease, CCHS, apparent life-threatening event, primary disorder of ANS dysregulation, or tumor of neural crest origin. This study was approved by the Rush University Medical Center and the University of Pittsburgh institutional review boards, and informed consent was obtained from all control subjects.

Genomic DNA was isolated from frozen frontal cortex brain tissue (SIDS cases) and blood (controls) samples utilizing standard methods. All coding regions and intron-exon boundaries in *PHOX2B* were amplified by polymerase chain reaction as described previously [Weese-Mayer et al., 2003b] and screened using direct sequencing methods [Garcia-Barcelo et al., 2003].

Standard χ^2 tests of independence were utilized for case-control comparisons for genotype/allele frequency and SIDS phenotype. Tests of gene-gene interaction were conducted using standard χ^2 tests of independence between genotype or allele frequency at two loci within the SIDS samples. No analyses were performed on the interaction between the *PHOX2B* intron 2 polymorphism and either the previously identified *5HTT* or *RET* mutations as the frequency of the *PHOX2B* intron 2 polymorphism would have driven the comparisons. When data were sparse (expected counts less than five in any cell), Fisher's exact test was used. Hardy-Weinberg equilibrium was confirmed by ethnicity in our control group for each of the polymorphic markers (*5HTT* promoter and intron 2, *PHOX2B* intron 2 and exon 3, and *RET* polymorphisms). Since this is a preliminary scan of variants for association with SIDS, only modest adjustments were made for multiple tests in order to cast a wide net for possible associations; significance was assigned to $P < 0.01$. All associations found in this study will need independent confirmation.

A single common polymorphism (IVS2 + 101A > G; g.1364A > G) was identified in intron 2 of the *PHOX2B* gene located 100 base pairs downstream of the exon 2 splice site (Table I). The genotype distributions for the intron 2 polymorphism differed

TABLE I. *PHOX2B* Intron 2 IVS2 + 101A > G in 91 SIDS Cases and 91 Matched Control Subjects

	Genotype distribution comparisons							Frequency of G allele		
	SIDS cases			Matched controls			<i>P</i> -values	SIDS cases	Matched controls	<i>P</i> -values
	AA	AG	GG	AA	AG	GG				
Caucasian	0.33	0.61	0.06	0.63	0.28	0.09	0.005	0.37	0.23	0.04
African-American	0.09	0.67	0.24	0.24	0.47	0.29	0.08	0.58	0.52	0.45
Total	0.21	0.64	0.15	0.44	0.37	0.19	0.0009	0.47	0.37	0.06

significantly between the SIDS cases and matched controls over the total dataset ($P=0.0009$) and between the Caucasian SIDS cases and controls ($P=0.005$), but did not reach significance in the African-American SIDS versus control comparison ($P=0.08$; Table I). Likely, the result is non-significant in the African-American group because of the high baseline frequency of this polymorphism in the African-American population, which significantly exceeds the frequency of the variant in the Caucasian population as seen in the control groups (Table I).

The allele frequency of the variant G allele for the intron 2 polymorphism was not significantly increased in the SIDS group relative to controls (Table I), although there was a strong trend towards higher G allele frequency in the SIDS group ($P=0.06$). The strong trend towards higher G allele frequency was further seen in the Caucasian SIDS group ($P=0.04$; Table I) compared to controls but was not observed in the comparison between African-American SIDS cases and controls ($P=0.45$). The difference in allele frequency does not reach significance because the homozygous GG genotype was more frequent in the control group, suggesting that the effect of this polymorphism on SIDS risk is relevant to presence or absence of the G allele and thus, is similar in the homozygous and heterozygous state.

Eight polymorphisms located in the third exon of the *PHOX2B* gene (Table II) occurred more frequently among SIDS cases (34 occurrences observed in 27/91 cases) than controls (19 occurrences observed in 16/91 controls) ($P=0.01$). Likewise, the number of occurrences among SIDS cases in the Caucasian and African-American subgroups was nearly double the number among their respective controls. Among SIDS cases containing a polymorphism in exon 3, 6/27 (22%) contained 2 or more polymorphisms compared to 2/16 (12%) controls (Table II). Each of the eight samples with two or more polymorphisms in exon 3 was from the African-American subgroup. Two of the eight

polymorphisms identified were protein-altering missense mutations (F153L and S176T), occurring in nine SIDS cases and four controls (10% and 4%, respectively; Table II).

All SIDS subjects demonstrated the normal genotype with both the 9 and 20 polyalanine-coding repeats on each chromosome of *PHOX2B*. Among controls, 1 African-American and 2 Caucasians were heterozygous for deletion variants containing 7, 14, and 15 repeats, respectively, as previously reported in control populations [Amiel et al., 2003; Weese-Mayer et al., 2003b; Toyota et al., 2004].

Gene-gene interaction (statistical non-independence between loci) between the *PHOX2B* exon 3 polymorphisms and the *5HTT* promoter L/L genotype or the L allele, or the *5HTT* intron 2 polymorphisms, was not found for SIDS risk, in comparisons of SIDS cases with controls or when the cohort was divided into ethnicity-specific subgroups. Gene interaction analysis revealed that of the 27 SIDS cases containing a *PHOX2B* exon 3 polymorphism(s), 3 also contained a *RET* mutation compared to 1/61 SIDS cases that contained no exon 3 polymorphism and were also tested for *RET* mutations ($P=0.07$). Three of 11 Caucasian SIDS cases with a *PHOX2B* exon 3 polymorphism had an additional *RET* mutation compared to 0/34 Caucasian SIDS cases containing no exon 3 polymorphism ($P=0.01$).

These results represent the first report describing specific polymorphisms in the *PHOX2B* gene that may confer SIDS risk and the analysis of these polymorphisms in relation to other mutations of ANS genes previously identified in these SIDS cases. Analysis of the *PHOX2B* gene in 91 SIDS cases and 91 matched controls revealed a single common polymorphism in intron 2, found more commonly among SIDS cases as compared to controls, as well as a group of 8 novel single nucleotide polymorphisms in exon 3 of *PHOX2B* occurring more frequently in SIDS cases than controls. The associations identified are consistent either with involvement of the specific

TABLE II. *PHOX2B* Exon 3 Polymorphisms in 91 SIDS Cases and 91 Matched Control Subjects

Location	Genotype	Amino acid effect	Number of patients with rare polymorphism					
			SIDS			Control		
			Caucasian	African-American	Total	Caucasian	African-American	Total
Exon 3	c.459T > G	F153L	0	1	1	2	0	2
Exon 3	c.526T > A	S176T	6	2	8	2	0	2
Exon 3	c.552C > T	Silent	1	2	3	0	2	2
Exon 3	c.642C > T	Silent	0	2	2	0	0	0
Exon 3	c.726A > G	Silent	0	2	2	0	1	1
Exon 3	c.750G > A	Silent	1	3	4	0	2	2
Exon 3	c.762A > C	Silent	1	7	8	1	5	6
Exon 3	c.870C > A	Silent	2	4	6	1	3	4
Total occurrences of polymorphisms			11	23	34	6	13	19

These polymorphisms were identified 34 times in the SIDS group compared to 19 times in the control group ($P=0.01$) and in 27/91 SIDS cases compared to 16/91 controls ($P=0.05$).

variants in SIDS, or with variants in genes in linkage disequilibrium with the tested variants.

Although the intron 2 polymorphism (IVS2 + 101A > G; g.1364A > G) identified in this study is a silent transition in the non-coding region of *PHOX2B*, it was recently linked with Hirschsprung disease (HSCR) [Garcia-Barcelo et al., 2003], another disease of ANS dysregulation. The Garcia-Barcelo report of a decreased frequency of the intron 2 polymorphism among 91 ethnic Chinese HSCR cases (19%) compared to 71 unmatched ethnic Chinese controls (36%) strengthens the conclusion that this intron 2 polymorphism is related to ANS dysfunction. It remains to be determined if the decreased frequency of the intron 2 polymorphism in *PHOX2B* among HSCR cases and the increased frequency among SIDS cases are related to a disease-specific factor (SIDS vs. HSCR) or an ethnicity factor (Caucasian/African-American vs. ethnic Chinese). The intron 2 polymorphism is located outside of the amino acid coding region of the *PHOX2B* gene and does not appear to be directly involved in *PHOX2B* splicing. However, the polymorphism could have other regulatory effects and may act in combination with mutations in genes involved in the *RET* and/or *EDNRB* signaling pathway to produce ANS dysfunction [Garcia-Barcelo et al., 2003].

Kijima et al. [2004] sequenced the *PHOX2B* gene in 23 Japanese SIDS cases and 50 controls and identified 1 polymorphism in exon 2 of *PHOX2B* and 2 intron 2 polymorphisms, none of which were identified in our study. These polymorphisms were identified in 1, 1, and 9% of subjects, respectively, but the authors do not clarify if these were identified in SIDS cases or controls. Conversely, none of the *PHOX2B* exon 3 polymorphisms that we describe in Caucasian and African-Americans were reported in the Japanese cases. This is likely due to the low frequency of occurrence, the small sample sizes, and ethnicity-specific issues.

The identification of polymorphisms in genes pertinent to the embryologic origin of the ANS in SIDS cases lends support to the overriding hypothesis that infants who succumb to SIDS have an underlying genetic predisposition. The polymorphisms identified in this study may be directly related to the SIDS phenotype but more likely are variations which, in association with mutations or polymorphisms elsewhere in the cascade of genes mediating ANS development, confer some level of susceptibility to phenotypes of ANS dysfunction including SIDS. The *MASH1-PHOX-RET* pathway, in which *PHOX2B* is needed for the expression of *RET*, has been shown to be an integral part of the development of both the sympathetic and enteric nervous systems [Pattyn et al., 1997]. The interaction of *PHOX2B* and *RET* in this pathway is consistent with our finding of a possible interaction between polymorphisms in these genes in mediating SIDS

risk, suggesting that genetic changes at multiple points in the pathway could combine to amplify risk.

It has recently been shown that *PHOX2B* plays a key role in the differentiation of central serotonergic neurons [Pattyn et al., 2003, 2004]. Coupled with the finding that two polymorphic regions of the serotonin transporter gene (*5HTT*) have been linked to SIDS [Narita et al., 2001; Weese-Mayer et al., 2003a,c] and demonstration of decreased serotonergic receptor binding in medullary regions of SIDS cases [Panigrahy et al., 2000], a potential relationship between the 5HT system, *PHOX2B*, and SIDS seems likely. We did not find any significant interactions between *PHOX2B* intron 2/exon 3 polymorphisms and the *5HTT* promoter/intron 2 polymorphisms. Thus, polymorphisms in *5HTT* and *PHOX2B* appear to exert independent effects on SIDS risk, potentially by acting on different aspects of 5HT system function.

While the results of this study are intriguing, the limitations of the study must be recognized. Specifically, the nature of the NIH-funded tissue bank requires anonymity of subjects with limited medical history provided, and it is limited in racial and ethnic representation. Further, the low frequency of occurrence of the polymorphisms found in exon 3 of *PHOX2B* makes comparison of these regions between cases and controls, and using gene interaction analysis difficult. To study polymorphisms with such a low rate of occurrence, it will be necessary to establish a larger sample size. Population stratification is a concern in any genetic association study and could be responsible for spurious associations in many association studies, including this one. Although there are statistical methods to account for hidden stratification [Devlin and Roeder, 1999; Pritchard et al., 2000], the most prudent approach when using an apparently stratified sample is to match cases and controls based on self-identified ethnicity. We are confident that our matched case-control sample adequately addresses any major concerns with stratification.

Although this study did not yield a SIDS-specific *PHOX2B* mutation, the identification of a common single nucleotide polymorphism associated with the SIDS phenotype, as well as the preponderance of coding region polymorphisms found in SIDS cases compared to controls, suggests that *PHOX2B* polymorphisms may imbue an increased risk for ANS dysfunction, including SIDS. The low rate of occurrence of mutations in *PHOX2B*, however, indicates that there are other yet unidentified genes and mutations responsible for the SIDS phenotype, either directly or in conjunction with the polymorphisms identified in *PHOX2B*, *RET*, *5HTT*, and/or other genes involved in ANS or serotonergic system development. Sequencing of additional genes involved in ANS or serotonergic development in a larger group of SIDS cases will be

expected to yield insight into the relationship between *PHOX2B*, additional candidate genes, and SIDS.

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REFERENCES

- Amiel J, Laudier B, Attie-Bitach T, Trang H, de Pontual L, Gener B, Trochet D, Etchevers H, Ray P, Simonneau M, Vekemans M, Munnich A, Gaultier C, Lyonnet S. 2003. Polyalanine expansion and frameshift mutations of the paired-like homeobox gene *PHOX2B* in congenital central hypoventilation syndrome. *Nat Genet* 33:459–461.
- Devlin B, Roeder K. 1999. Genomic control for association studies. *Biometrics* 55:997–1004.
- Franco P, Szliwowski H, Dramaix M, Kahn A. 1998. Polysomnographic study of the autonomic nervous system in potential victims of sudden infant death syndrome. *Clin Auton Res* 8:243–249.
- Franco P, Szliwowski H, Dramaix M, Kahn A. 1999. Decreased autonomic responses to obstructive sleep events in future victims of sudden infant death syndrome. *Pediatr Res* 46:33–39.
- Garcia-Barcelo M, Sham MH, Lui VC, Chen BL, Ott J, Tam PK. 2003. Association study of *PHOX2B* as a candidate gene for Hirschsprung disease. *Gut* 52:563–567.
- Hirsch MR, Tiveron MC, Guillemot F, Brunet JF, Goridis C. 1998. Control of noradrenergic differentiation and *Phox2a* expression by *MASH1* in the central and peripheral nervous system. *Development* 125:599–608.
- Kijima K, Sasaki A, Niki T, Umetsu K, Osawa M, Matoba R, Hayasaka K. 2004. Sudden infant death syndrome is not associated with the mutation of *PHOX2B* gene, a major causative gene of congenital central hypoventilation syndrome. *Tohoku J Exp Med* 203:65–68.
- Lo L, Tiveron MC, Anderson DJ. 1998. *MASH1* activates expression of the paired homeodomain transcription factor *Phox2a*, and couples pan-neuronal and subtype-specific components of autonomic neuronal identity. *Development* 125:609–620.
- Lo L, Morin X, Brunet JF, Anderson DJ. 1999. Specification of neurotransmitter identity by *Phox2* proteins in neural crest stem cells. *Neuron* 22:693–705.
- Marazita ML, Maher BS, Cooper ME, Silvestri JM, Huffman AD, Smok-Pearsall SM, Kowal MH, Weese-Mayer DE. 2001. Genetic segregation analysis of autonomic nervous system dysfunction in families of probands with idiopathic congenital central hypoventilation syndrome. *Am J Med Genet* 100:229–236.
- Matera I, Bachetti T, Puppo F, Di Duca M, Morandi F, Casiraghi GM, Cilio MR, Hennekam R, Hofstra R, Schober JG, Ravazzolo R, Ottonello G, Ceccherini I. 2004. *PHOX2B* mutations and polyalanine expansions correlate with the severity of the respiratory phenotype and associated symptoms in both congenital and late onset Central Hypoventilation syndrome. *J Med Genet* 41:373–380.
- Narita N, Narita M, Takashima S, Nakayama M, Nagai T, Okado N. 2001. Serotonin transporter gene variation is a risk factor for sudden infant death syndrome in the Japanese population. *Pediatrics* 107:690–692.
- Panigrahy A, Filiano J, Sleeper LA, Mandell F, Valdes-Dapena M, Krous HF, Rava LA, Foley E, White WF, Kinney HC. 2000. Decreased serotonergic receptor binding in rhombic lip-derived regions of the medulla oblongata in the sudden infant death syndrome. *J Neuropathol Exp Neurol* 59:377–384.
- Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF. 1997. Expression and interactions of the two closely related homeobox genes *Phox2a* and *Phox2b* during neurogenesis. *Development* 124:4065–4075.
- Pattyn A, Morin X, Cremer H, Goridis C, Brunet JF. 1999. The homeobox gene *Pbox2b* is essential for the development of autonomic neural crest derivatives. *Nature* 399:366–370.
- Pattyn A, Vallstedt A, Dias JM, Samad OA, Krumlauf R, Rijli FM, Brunet JF, Ericson J. 2003. Coordinated temporal and spatial control of motor neuron and serotonergic neuron generation from a common pool of CNS progenitors. *Genes Dev* 17:729–737.
- Pattyn A, Simplicio N, van Doorninck JH, Goridis C, Guillemot F, Brunet JF. 2004. *Ascl1/Mash1* is required for the development of central serotonergic neurons. *Nat Neurosci* 7:589–595.
- Ponsonby AL, Dwyer T, Gibbons LE, Cochrane JA, Jones ME, McCall MJ. 1992. Thermal environment and sudden infant death syndrome: Case-control study. *BMJ* 304:277–282.
- Pritchard JK, Stephens M, Rosenberg NA, Donnelly P. 2000. Association mapping in structured populations. *Am J Hum Genet* 67:170–181.
- Sasaki A, Kanai M, Kijima K, Akaba K, Hashimoto M, Hasegawa H, Otaki S, Koizumi T, Kusuda S, Ogawa Y, Tuchiya K, Yamamoto W, Nakamura T, Hayasaka K. 2003. Molecular analysis of congenital central hypoventilation syndrome. *Hum Genet* 114:22–26.
- Schechtman VL, Harper RM, Kluge KA, Wilson AJ, Hoffman HJ, Southall DP. 1988. Cardiac and respiratory patterns in normal infants and victims of the sudden infant death syndrome. *Sleep* 11:413–424.
- Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni ED, Perticone F, Rosti D, Salice P. 1998. Prolongation of the QT interval and the sudden infant death syndrome. *N Engl J Med* 338:1709–1714.
- Toyota T, Yoshitsugu K, Ebihara M, Yamada K, Ohba H, Fukasawa M, Minabe Y, Nakamura K, Sekine Y, Takei N, Suzuki K, Itokawa M, Meerabux JM, Iwayama-Shigeno Y, Tomaru Y, Shimizu H, Hattori E, Mori N, Yoshikawa T. 2004. Association between schizophrenia with ocular misalignment and polyalanine length variation in *PMX2B*. *Hum Mol Genet* 13:551–561.
- Trochet D, O'Brien LM, Gozal D, Trang H, Nordenskjold A, Laudier B, Svensson PJ, Uhrig S, Cole T, Niemann S, Munnich A, Gaultier C, Lyonnet S, Amiel J. 2005. *PHOX2B* genotype allows for prediction of tumor risk in congenital central hypoventilation syndrome. *Am J Hum Genet* 76:421–426.
- Weese-Mayer DE, Berry-Kravis EM, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003a. Sudden infant death syndrome: Association with a promoter polymorphism of the serotonin transporter gene. *Am J Med Genet Part A* 117A:268–274.
- Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003b. Idiopathic congenital central hypoventilation syndrome: Analysis of genes pertinent to early autonomic nervous system embryologic development and identification of mutations in *PHOX2B*. *Am J Med Genet Part A* 123A:267–278.
- Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML. 2003c. Association of the serotonin transporter gene with sudden infant death syndrome: A haplotype analysis. *Am J Med Genet Part A* 122A:238–245.
- Weese-Mayer DE, Berry-Kravis EM, Zhou L, Maher BS, Curran ME, Silvestri JM, Marazita ML. 2004. Sudden infant death syndrome: Case-control frequency differences at genes pertinent to early autonomic nervous system embryologic development. *Pediatr Res* 56:391–395.
- Willinger M, James LS, Catz C. 1991. Defining the sudden infant death syndrome (SIDS): Deliberations of an expert panel convened by the National Institute of Child Health and Human Development. *Pediatr Pathol* 11:677–684.