May 2004 | Volume 1 | Issue 9

JOHNS HOPKINS MEDICINE | JOHNS HOPKINS NURSING
The Institute for Johns Hopkins Nursing

eNeonatal Review

supported by an unrestrictededucational grant from Forest Pharmaceuticals, Inc.

COURSE DIRECTORS

Edward E. Lawson, M.D.
Professor
Department of Pediatrics – Neonatology
The Johns Hopkins University School of Medicine

Christoph U. Lehmann, M.D.
Assistant Professor
Department of Pediatrics – Neonatology
The Johns Hopkins University School of Medicine

Lawrence M. Nogee, M.D.
Associate Professor
Department of Pediatrics – Neonatology
The Johns Hopkins University School of Medicine

Lorraine A. Harbold, R.N., M.S.
The Johns Hopkins Hospital;
NICU Education Coordinator

PROGRAM INFORMATION

CE Info
Accreditation
Credit Designation
Target Audience
Learning Objectives
Faculty Disclosure
Disclaimers

Recommend to a Colleague

LENGTH OF ACTIVITY
0.5 hours

EXPIRATION DATE
May 15, 2005

NEXT ISSUE
June 15, 2004

Post-Test

In this issue... Volume 1, Number 9

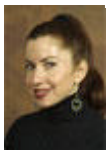
Clinicians are often confronted by infants with enigmatic complex disorders. The focus of this edition is on two vexing diseases: Sudden Infant Death Syndrome (SIDS) and the less common but equally complex Congenital Central Hypoventilation Syndrome (CCHS).

As SIDS was discussed in detail in a prior eNeonatology issue, the focus herein will be exclusively on studies directed toward understanding its genetic basis. CCHS, reviewed in detail on-line at www.GeneReviews.org and in the ATS Statement on CCHS, has also been recently reviewed for the pulmonary literature (1). The rationale for addressing these topics in this issue is to encourage the reader to consider an analytical approach based on published clinical symptoms and identified neuropathological studies.

Reviews & Commentary:
Debra E. Weese-Mayer, M.D.
Brion Maher, Ph.D.

Guest Editors of the Month

Debra E. Weese-Mayer, M.D.
Professor of Pediatrics
Director, Pediatric Respiratory Medicine
Rush University
Chicago, Illinois



Brion Maher, Ph.D.
Assistant Professor of Oral Medicine and Pathology
University of Pittsburgh
School of Dental Medicine
Baltimore, Maryland

Guest Faculty Disclosures

Debra E. Weese-Mayer, M.D.
Faculty Disclosure: Dr Weese-Mayer discloses that she has received grants from The CJ Foundation for SIDS, The Rett Syndrome Research Foundation and The Dysautonomia Foundation

Brion Maher, Ph.D.
Faculty Disclosure: Dr. Maher discloses that he receives Grants and Research support from The Nathan Cummings Fund.

Unlabelled/Unapproved Uses

No faculty member has indicated that their presentation will include information on off label products.

COMMENTARY

The introduction of the aggressive "Back to Sleep" campaign in 1992 targeted identified modifiable environmental risk factors for SIDS and led to a decrease in SIDS incidence from 1.2 per 1000 live births (2) to 0.55 per 1000 live births in 2001 (3). Despite this decline, African American infants maintained a higher SIDS incidence as well as a slower decline when compared with Caucasian infants (2,3). Further, infants of all ethnic groups continue to succumb to SIDS despite full compliance with known modifiable risk factors. These observations led investigators to consider the possibility of gene-by-environment interaction (whereby an environmental condition or toxin impacts gene expression) as an explanation for the remaining 2,234 U.S. infants dying from SIDS in 2001 (3).

Although the etiology of SIDS remains unresolved and the variation in incidence by ethnicity remains unexplained, recent data may illuminate both issues. Key research published prior to the studies reviewed herein includes the work by Schwartz et al. (4,5) describing prolongation of the QT interval in SIDS. Among 34,000 infants in whom an EKG was performed at 3-4 days of age, Schwartz et al identified 24 infants who subsequently died of SIDS. Twelve of these SIDS victims exhibited a long corrected QT interval(44ms or more). These authors also reported a 44 day-old infant, with a prolonged QT interval (648ms) and an SCN5A missense mutation (5), who responded to cardiac defibrillation after cardiac arrest. The long QT syndrome is a primary cardiac channelopathy with 5 identified cardiac ion channel genes implicated. Defects in the cardiac sodium channel gene SCN5A account for up to 10% of the long QT syndrome cases and individuals with SCN5A mutations are known to have an increased risk of cardiac events during sleep.

In SIDS, arrhythmias secondary to prolonged QT intervals may account for a small fraction of deaths; Dr. Ackerman's tactic of studying the cardiac sodium channel gene (SCN5A) in SIDS extends our profession's knowledge base in this area.

With regard to the neuropathologic findings in SIDS, in the U.S. Panigrahy et al. (6) reported a decrease in serotonergic receptor binding in the arcuate nucleus, n. raphé obscurus, and other medullary regions that contain serotonergic cell bodies. Similarly, Ozawa and Okado (7) reported a decrease in serotonergic receptor binding in the dorsal nucleus of the vagus, solitary nucleus and ventrolateral medulla in SIDS cases in Japan. With regard to clinical symptomatology in SIDS cases, dysfunction of the autonomic nervous system has been recognized. Because serotonin influences a broad range of physiological systems including the regulation of breathing, the cardiovascular system, temperature, and sleep-wake cycles, it follows that serotonin might play a regulatory role in SIDS.

The gene that seems of greatest interest based upon the neuropathologic studies is the serotonin transporter gene (5-HTT). This gene regulates the duration and strength of the interactions between serotonin (5-HT) and its receptors by controlling re-uptake of 5-HT from the

extracellular space. Two polymorphisms in the 5' regulatory region of the 5-HTT gene have been shown to differentially modulate gene expression. One of these is an insertion/deletion repeat sequence in the promoter region of the 5-HTT gene and the other is a variable number tandem repeat (VTNR) in intron 2 of the 5-HTT gene. Further, recognition that the 5-HTT promoter allele distribution varies widely by ethnicity provides potential explanations for apparent ethnic group disparities in SIDS incidence.

The work of Narita et al. and Weese-Mayer et al. in investigating reports of decreased serotonergic receptor binding in brainstem centers pertinent to respiratory control among SIDS cases sheds new light on the importance of the serotonin transporter gene.

Congenital central hypoventilation syndrome(CCHS), first described in 1970, is an unique disorder of respiratory control that occurs in association with Hirschsprung disease and tumors of neural crest origin (neuroblastoma, ganglioneuroblastoma, ganglioneuroma)(8). CCHS also occurs with symptoms of diffuse autonomic nervous system dysfunction/dysregulation (ANSD) (8,9). Subsequently, symptoms of ANSD have been identified in nuclear family members of the probands with CCHS, though the relatives of the CCHS cases tend to manifest a milder spectrum with fewer symptoms and/or systems than the cases (9). CCHS is thought to be genetic in origin based upon familial recurrence data and genetic segregation analyses. Pursuit of the genetic basis for CCHS by molecular genetic analysis has been limited due to the rarity of the disease (fewer than 300 recognized cases worldwide). To date, most studies have also been limited to the study of genes specifically related to Hirschsprung disease. Twenty patients have been reported with unique protein-altering mutations in these genes: eight unrelated patients with mutations in RET (10-14); one patient with a mutation in GDNF (10); one patient with a mutation in EDN3 (15); one patient with a mutation in BDNF (16); five patients with mutations in HASH1 (13,17); one patient with a mutation in PHOX2a (13); one patient with a mutation in GFRA1 (13); one patient with a mutation in BMP2 (18); and one patient with a mutation in ECE1 (18).

Based upon the varying results, none of the above-described genes accounted for a substantial number of CCHS cases or appeared to be pathogenic. However, the PHOX2b gene was investigated based upon its role in the early embryologic origin of the ANS. As the reader reviews the cited literature in the next section, a distinct variation in percent of affected individuals with presumed CCHS will become apparent by site of study. Variation in the percent of affected individuals with a PHOX2b mutation could be attributed to differences in the clinical diagnostic criteria for CCHS or inclusion of patients with phenocopies of CCHS (i.e., Hirschsprung disease with autonomic dysfunction who also have alveolar hypoventilation). These data indicate that the clinical symptom-directed genetic investigation has proven effective. The next approach will be to establish a more detailed correlation between the number of extra polyalanine repeats on the affected allele and the phenotype.

The studies on autonomic nervous system dysfunction by Amiel et al., Weese-Mayer et al., and Sasaki et al. point to interesting new connections between the clinical phenotype and the genetic basis for disease in CCHS. Prior to the cited references, a comprehensive gene-directed approach to these two diseases had not been reported.

Highlighting these publications emphasizes the point that major progress in the study of both SIDS and CCHS has come about as the result of the study of genes that could (logically) explain clinical and neuropathological findings. This "likely genetic candidate" approach may be applicable in investigating some of the other complex and seemingly undecipherable diseases that affect infants and children.

References

1. Weese-Mayer DE, Berry-Kravis EM. 2004. Genetics of Congenital central hypoventilation

syndrome: Lessons from a seemingly orphan disease. Am J Respir Crit Care Med doi: 10.1164/rccm.200402-245PP in press.

2. Kochanek KD, Hudson BL. 1995. Advance Report of Final Mortality Statistics, 1992. Monthly Vital Statistics Report 43(6) Supplement. Hyattsville, MD: National Center for Health Statistics.

3. Arias E, MacDorman MF, Strobino DM, Guyer B. 2003. Annual summary of vital statistics-2002. Pediatrics 112(6):1215-1230.

4. Schwartz PJ, Stramba-Badiale M, Segantini A, Austoni P, Bosi G, Giorgetti R, Grancini F, Marni E, 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.

5. Schwartz PJ. Priori SG. Dumaine R. Napolitano C. Antzelevitch C. Stramba-Badiale M. Richard TA. Berti MR. Bloise R. 2000. A molecular link between the sudden infant death syndrome and the long-QT syndrome. N Engl J Med. 343(4):262-267.

6. Panigrahy A, Filiano J, Sleeper LA, Mandell F, Valdes-Dapena M, Krous HF, Rava LA, Foley E, White WF, Kinney HC. 2000. Decreased serotonin receptor binding in rhombic lip-derived regions of the medulla oblongata in the sudden infant death syndrome. J Neuropathol and Exper Neurol. 59:377-384.

7. Ozawa Y, Okado N. 2002. Alteration of serotonergic receptors in the brain stems of human patients with respiratory disorders. Neuropediatr 33: 142-149.

8. Weese-Mayer DE, Shannon DC, Keens TG, Silvestri JM. 1999. American Thoracic Society Statement. Idiopathic congenital central hypoventilation syndrome. Diagnosis and management. Am J Respir Crit Care Med. 160:368-373.

9. Weese-Mayer DE, Silvestri HM, Huffman AD, Smok-Pearsall SM, Kowal MH, Maher BS, Cooper ME, Marazita ML. 2001. Case/Control family study of ANS dysfunction in idiopathic congenital central hypoventilation syndrome. Am J Med Genet. 100:237-245.

10. Amiel J, Salomon R, Attié T, Pelet A, Trang H, Mokhtari M, Gaultier C, Munnich A, Lyonnet S. 1998. Mutations of the RET-GDNF signaling pathway in Ondine's curse. Am J Hum Genet. 62:715-717.

11. Sakai T, Wakizaka A, Matsuda H, Nirasawa Y, Itoh Y. 1998. Point mutation in exon 12 of the receptor tyrosine kinase proto-oncogene RET in Ondine-Hirschsprung syndrome. Pediatrics. 101:924-926.

12. Sakai T, Wakizaka A, Nirasawa Y. 2001. Congenital central hypoventilation syndrome associated with Hirschsprung's disease: Mutation analysis of the RET and endothelin-signaling pathways. Eur J Pediatr Surg. 11:335-337.

13. 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 Gen. 114:22-26.

14. Fitze G, Paditz E, Schlafke M, Kuhlisch E, Roesner D, Schackert HK. 2003. Association of germline mutations and polymorphisms of the RET proto-oncogene with idiopathic congenital central hypoventilation syndrome in 33 patients. J Med Gen. 40:E10.

15. Bolk, S, Angrist M, Xie J, Yanagisawa M, Silvestri JM, Weese-Mayer DE, Chakravarti A. 1996. Endothelin-3 frameshift mutation in congenital central hypoventilation syndrome. Nature Gen. 13:395-396

16. Weese-Mayer DE, Bolk S, Silvestri JM, Chakravarti A. 2002. Idiopathic congenital central hypoventilation syndrome: Evaluation of brain-derived neurotrophic factor genomic DNA sequence variation. Am J Med Gen. 107:306-310.

17. de Pontual L, Nepote V, Attie-Bitach T, Al Halabiah H, Trang H, Elghouzzi V, Levacher B, Benihoud K, Auge J, Faure C, Laudier B, Vekemans M, Munnich A, Perricaudet M, Guillemot F, Gaultier C, Lyonnet S, Simonneau M, Amiel J. 2003. Noradrenergic neuronal development is impaired by mutation of the proneural HASH-1 gene in congenital central hypoventilation syndrome (Ondine's curse). Hum Mol Gen. 12:3173-80.

18. Weese-Mayer DM, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003. 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 Gen. 123A:267-278.

SIDS: SCN5A MUTATIONS

Ackerman MJ. Siu BL. Sturner WQ. Tester DJ. Valdivia CR. Makielski JC. Towbin JA. 2001. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. JAMA. 286(18):2264-9.

Functional mutations in the gene encoding the cardiac sodium channel SCN5A were found in 2 of 93 (2%) of SIDS/sudden unexpected sudden infant death cases.

Ackerman and colleagues used a candidate approach to search for genetic variants influencing the risk for SIDS. Their candidate gene of choice for their analyses was SCN5A, the gene that codes for the cardiac sodium channel. This choice was particularly germane to SIDS, as additional evidence supports a role for SCN5A mutations in cardiac events during sleep.

A two-fold approach to examining the role of SCN5A in SIDS was used in a sample of 93 SIDS/ sudden unexpected infant death cases identified at the Medical Examiner's Office of the Arkansas State Crime Lab from September 1997 to August 1999. First, DNA extracted from the SIDS cases and 400 ethnically representative (~25% African-American) controls was analyzed for the presence of SCN5A mutations. Second, mutations that were discovered via screening were assayed for potential functional significance.

Ackerman and colleagues discovered two mutations - an alanine to serine at position 997 and an arginine to histidine at position 1826 - that were not present in any of the 400 control subjects screened. When transfected into human embryonic kidney cells, which lack intrinsic electrical currents, each mutant type exhibited marked electrophysiological changes when compared to the wild type SCN5A transfected cells.

In summary, approximately 2% of the SIDS/sudden unexpected infant death cases examined by the researchers had potentially functional mutations in SCN5A that were not present in controls. The authors conclude that these mutations, or other mutations in SCN5A, may be responsible for lethal arrhythmia in at least a small proportion of SIDS cases.

Ackerman MJ. Siu BL. Sturner WQ. Tester DJ. Valdivia CR. Makielski JC. Towbin JA. 2001. Postmortem molecular analysis of SCN5A defects in sudden infant death syndrome. JAMA. 286(18):2264-9.

(For non-journal subscribers, an additional fee may apply for full text article)

view journal abstract view full article back to top

SIDS: 5-HTT POLYMORPHISM

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.

The long allele of the serotonin transporter promoter polymorphism was significantly increased in frequency among 27 SIDS cases (22.2%) vs. 115 controls (13.5%).

Serotonin (5-HT) influences a variety of physiological systems that may be functionally dysregulated in children at risk for SIDS. Although the serotonergic system is extensive, the function of serotonin is limited by the action of a single protein, the serotonin transporter (5-HTT). Motivated by this evidence, Narita and colleagues examined the role of a functional polymorphism in the promoter region of the 5-HTT gene in SIDS risk. Their sample consisted of 27 Japanese SIDS cases and 115 age-matched controls. The investigators genotyped the promoter insertion/ deletion polymorphism in cases and controls to test the hypothesis that cases differ from controls in allele and/or genotype frequency.

The polymorphism is generally considered to consist of two common alleles: the short (14 copies of the 20-23 base pair unit) and long (16 copies of the 20-23 base pair unit) alleles. Other gene expression studies have shown that individuals with the long allele tend to exhibit increased transcription of 5-HTT. Since the serotonin transporter functions in serotonin reuptake from the synaptic cleft, increased 5-HTT activity would result in a decrease in free 5-HT.

Narita et colleagues found a significant increase in the presence of the long allele in SIDS cases (22.2%) vs. controls (13.5%). Additionally, they found 3 extra long (XL) alleles in SIDS cases (5.6%) vs. 1 in controls (0.4%). The investigators state that they found low levels of 5-HT in the blood of individuals with the XL allele, thus supporting the notion that, like the long allele, the XL allele may be a more effective promoter of 5-HTT transcription.

Overall, the results of this study provided the first highly significant evidence for the role of a specific gene in SIDS risk.

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.

(For non-journal subscribers, an additional fee may apply for full text article)

view journal abstract view full article back to top

SIDS: ETHNIC VARIATIONS IN 5-HTT POLYMORPHISM

Weese-Mayer DE, Berry-Kravis EM, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003. Sudden infant death syndrome: Association with a promoter polymorphism of the serotonin transporter gene. Am J Med Gen. 117A:268-274.

Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML. 2003. Association of the serotonin transporter gene with sudden infant death syndrome: A haplotype analysis. Am J Med Gen. 122A:238-245.

The first publication demonstrated an increased presence of the long allele for 5-HTT promoter in SIDS cases as compared to controls, though subgroup significance was restricted to Caucasians. A second polymorphism, in intron 2 of the 5-HTT gene, was also found to be associated with SIDS in the African American SIDS cases. This work is of particular importance because both the frequency of the long allele of the 5-HTT promoter polymorphism and the rate of SIDS vary widely by ethnicity, with the SIDS-related long alleles of both polymorphisms being more prevalent in

African Americans and the incidence of SIDS being highest in African Americans (compared to Caucasians and Hispanics).

Weese-Mayer and colleagues replicated the finding of an increase in frequency of the long allele of the 5-HTT promoter insertion/deletion polymorphism in SIDS cases in an independent sample of 87 SIDS cases (43 African-American and 44 Caucasian) and 87 sex/ethnicity-matched controls. The investigators found significant differences in both genotype and allele frequency distribution in the combined (African-American and Caucasian) dataset; in addition, allele frequency in the Caucasian dataset, with the long allele and its genotypes, increased in the SIDS cases vs. controls. While the results were not statistically significant within the African American subgroup comparisons and for genotype within the Caucasian subgroup comparisons (possibly due to small sample size and consequent decreased statistical power), there was a trend toward increased frequency of the long allele in the African American SIDS cases and genotypes containing the long allele in the Caucasian SIDS cases.

In addition to the case-control results, Weese-Mayer et al. examined allele and genotype frequency differences by ethnicity in an additional set of 334 control subjects. The frequency of the long allele was increased in African-Americans (73.9%) vs. Caucasians (53%). This second publication reports that a second polymorphism in intron 2 of the 5-HTT gene (wherein a variable number of tandem repeats [VNTR] of the intron are present) is differentially distributed among ethnic groups in their SIDS and Control cohorts. Similar to the promoter polymorphism, the long (12-copy) allele of the intron 2 VNTR has been experimentally demonstrated to be a more efficient promoter of 5-HTT transcription.

The intron 2 and promoter VNTRs were genotyped in the 90 SIDS cases and sex/ethnicity-matched controls. The frequency of the 12-repeat allele of the intron 2 VNTR was significantly increased among the African American (85.2%) SIDS cases compared to the Caucasian SIDS cases (59.8%), and among African American (70.4%) controls compared to Caucasian (57.6%) controls. Furthermore, analyses of the promoter-intron 2 haplotypes (two-locus genotypes) revealed a similar pattern. The L-12 haplotype ("long" allele present at the promoter and "12" allele present at intron 2 on the same chromosome) was increased in frequency in SIDS cases vs. controls, and among African American SIDS cases vs. controls, but not Caucasian SIDS cases vs. controls.

Weese-Mayer and colleagues concluded that not only may the promoter polymorphism of the 5-HTT gene play an important role in SIDS risk but also it may explain, in part, the ethnic differences in SIDS risk. Specifically, we know that the SIDS rates are high among African Americans and low among Japanese, and that the 5-HTT long allele frequency is high among African Americans and low among Japanese controls, thereby potentially explaining the heightened SIDS incidence among African Americans in contrast to the low incidence among the Japanese. Further, the definition of SIDS risk using the promoter-intron 2 haplotype may be more precise or pronounced in African Americans vs. Caucasians.

Weese-Mayer DE, Berry-Kravis EM, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003. Sudden infant death syndrome: Association with a promoter polymorphism of the serotonin transporter gene. Am J Med Gen. 117A:268-274.

Weese-Mayer DE, Zhou L, Berry-Kravis EM, Maher BS, Silvestri JM, Marazita ML. 2003. Association of the serotonin transporter gene with sudden infant death syndrome: A haplotype analysis. Am J Med Gen. 122A:238-245.

(For non-journal subscribers, an additional fee may apply for full text article)

view journal abstract view full article back to top

CCHS: PHOX2b MUTATIONS

Amiel J, Laudier B, Attié-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. Nature Genetics. 33:459-461 and appendix.

A polyalanine repeat expansion of the PHOX2b gene is found in 62% of CCHS cases, and other mutations in PHOX2b are found in 7% of CCHS cases, but both mutations are absent in controls.

Amiel and colleagues used a candidate gene approach to their search for CCHS susceptibility genes. They noted that previous genetic findings in CCHS have been low penetrant mutations, seemingly insufficient to cause disease. Thus, they attempted to identify additional genetic mutations that may be more predictive for CCHS in their 29 patients. Because of the wide range of deficits in the autonomic nervous system (ANS) among children with CCHS, these investigators focused their attention on ***PHOX2b***, a gene whose protein is a highly conserved transcription factor and which is known to play a key role in the development of ANS reflex circuits in mice.

PHOX2b, located on chromosome 4p12, encodes a protein that usually contains two polyalanine repeat sequences of 9 and 20 residues in length. These polyalanine repeat lengths are conserved between mice and humans, suggesting that disruption may cause a critical alteration in function. Amiel and colleagues found variations or mutations in ***PHOX2b*** in 22 of 29 (69%) CCHS cases. In 20 of these cases(62%), a variable expansion of the 20 residue polyalanine tract was found. They concluded that each of these expansions must have occurred de novo since the expansions varied in length and were not present on mutation screening in the 8 sets of parents of the CCHS cases. In addition to the polyalanine repeat expansion, they found 2 of 29 (7%) CCHS cases with unique frameshift mutations. None of these ***PHOX2b*** expansion mutations were present in controls.

In the same publication, Amiel et al demonstrated the presence of ***PHOX2b*** expression in early developmental human embryos, in both central autonomic neuron circuits and in peripheral neural crest derivatives.

Amiel and colleagues concluded that ***PHOX2b*** plays a central role in the development and/or function of the neuronal network involved in autonomic regulation of respiration, and that mutations in ***PHOX2b*** may result in CCHS. This publication is of great importance as it identifies the first gene found by ANS-related function (in contrast to Hirschsprung disease association) in CCHS. The fact that 69% of CCHS cases demonstrated mutations in this gene is impressive.

Amiel J, Laudier B, Attié-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. Nature Genetics. 33:459-461 and appendix.

(For non-journal subscribers, an additional fee may apply for full text article)

view journal abstract view full article back to top

CCHS: CONFIRMING PHOX2b MUTATION

Weese-Mayer DM, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003. 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 Gen. 123A:267-278.

Confirming the findings of Amiel et al., in this study, polyalanine repeat expansions of the PHOX2b gene were observed in 97% of cases, and another PHOX2b mutation was found in one of the remaining two cases, while control patients had no polyalanine expansion mutations. Autosomal dominant transmission of the repeat expansion to CCHS offspring was observed from both CCHS case parents and from parents with a mosaic pattern for the mutation.

Weese-Mayer and colleagues selected a set of candidate genes involved in ANS development for mutation screening via direct DNA sequencing in a set of 67 CCHS cases and gender/ethnic-matched controls. The genes screened included mammalian achaete-scute homolog-1 (***MASH1***), bone morphogenic protein-2 (***BMP2***), engrailed-1 (***EN1***), ***TLX3***, endothelin converting enzyme-1 (***ECE1***), endothelin-1 (***EDN1***), and ***PHOX2a***. Although novel mutations were found in a subset of these genes, none occurred with adequate frequency to represent disease-causing mutations.

Subsequent work focused on the previously defined ***PHOX2b*** polyalanine repeat expansion. The researchers found the exon 3 polyalanine repeat expansion in 65 of their 67 (97%) CCHS probands. An association between polyalanine repeat (mutation) length and the severity of autonomic dysfunction (number of ANSD symptoms) was also found. In the two remaining cases: a nonsense mutation (premature stop codon) in ***PHOX2b*** was identified in one patient and a previously reported frameshift point mutation in ***EDN3*** was each present in the second patient.

Screening in 97 parents revealed 4 parents who appeared to demonstrate mosaicism for the repeat polyalanine expansion, suggesting that not all CCHS causing mutations occur ***de novo.*** Moreover, the polyalanine repeat expansion was studied in 4 women with CCHS who have one child each. In the 3 cases where the child has the CCHS phenotype, the mother passed her expanded allele to the affected child, thus supporting dominant inheritance of CCHS in these cases.

Further, this study establishes a clinically available assay for the diagnosis of CCHS (genetests.org).

Weese-Mayer DM, Berry-Kravis EM, Zhou L, Maher BS, Silvestri JM, Curran ME, Marazita ML. 2003. 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 Gen. 123A:267-278.

(For non-journal subscribers, an additional fee may apply for full text article)

view journal abstract view full article back to top

CCHS: PHOX2b & ANS

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 Gen. 114:22-26.

A polyalanine repeat expansion of the PHOX2b gene is found in 4 of 10 (40%) CCHS cases and another mutation in PHOX2b is found in 1 of 10 (10%) CCHS cases, but is absent in controls. Just as in Weese-Mayer et al. (2003), other genes pertinent to the early embryologic origin of the ANS were studied without clear disease-defining genes.

In a study of seven cases with isolated CCHS and 3 cases with Hirschsprung Disease and CCHS, Sasaki and colleagues screened, by direct DNA sequencing, ten genes involved in the development of the brain's respiratory center: ***RET***, ***GDNF***, ***GFRA1***, ***PHOX2A***, ***PHOX2B***, ***HASH-1***, ***EDN1***, ***EDN3***, ***EDNRB***, and ***BDNF***.

Sasaki and colleagues detected ***PHOX2b*** polyalanine repeat expansions in 4 of 10 CCHS (40%) cases and a ***PHOX2b*** insertion frameshift mutation in 1 of 10 (10%) CCHS cases, but not in any of 50 controls screened. All cases were Japanese. Parents were available for two cases of CCHS

(both with the ***PHOX2b*** polyalanine repeat expansion), but they lacked the expansion mutations indicating that in these families these mutations were ***de novo***.

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 Gen. 114:22-26.

(For non-journal subscribers, an additional fee may apply for full text article)

view journal abstract view full article back to top

Click here to go to the Post-Test and receive CE credit

Recommend eNeonatal Review to a colleague

View this newsletter as a downloadable PDF

Accreditation back to top

Physicians

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Nurses

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Credit Designations back to top

Physicians

The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.5 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Nurses

The Institute for Johns Hopkins Nursing designates this activity for a maximum of 0.5 contact hours for this eNewsletter.

Respiratory Therapists

Contact your state licensing board to confirm that AMA PRA category 1 credits are accepted toward fulfillment of RT requirements.

Target Audience back to top

This activity has been developed for Neonatologists, NICU Nurses and Respiratory Therapists working with Neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives back to top

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity. At the conclusion of this activity, participants should be able to:

- Develop a more complete understanding of the results of the on-going research into potential genetic markers for SIDS and CCHS.
- Understand how these genotypes may explain the observed ethnic differences in the incidence of SIDS.
- Evaluate, based on the results discussed, the value of a candidate gene approach to identifying key causative factors of these conditions.

Faculty Disclosure Policy Affecting CE Activities back to top

As sponsors accredited by the Accreditation Council for Continuing Medical Education and American Nursing Credentialing Center, it is the policy of The Johns Hopkins University School of Medicine and The Institute of Johns Hopkins Nursing to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed an education presentation. The presenting faculty reported the following:

- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/ material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

Unlabelled/Unapproved Uses back to top

In accordance with the ACCME and ANCC Standards for Commercial Support, the audience is advised that one or more presentations in this continuing education activity may contain reference(s) to unlabeled or unapproved uses of drugs or devices.

No faculty member has indicated that their presentation will include information on off label products.

Disclaimers back to top

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of The Johns Hopkins University name implies

review of education format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

Internet CE Policy back to top

The Offices of Continuing Education (CE) at The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

The Johns Hopkins University School of Medicine and The Institute For Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet based program. Your information will never be given to anyone outside The Johns Hopkins University program. CE collects only the information necessary to provide you with the service you request.

Copyright