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Finding Genetic Mechanisms in Syndromes of Sleep Disordered Breathing

Report to the RNS Assembly and the ATS Board from the ad hoc Committee on Inheritance and Ventilatory Control

Approved by the ATS Board of Directors July 11, 1999

MENU		
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Rationale. The tools of the Human Genome Project will offer opportunity for experiments to address the molecular basis for disorders of ventilatory control. In other fields, there are successful models for gene discovery not only for monogenic disorders but also for illnesses with complex pathophysiology. Finding genes for the disorders of respiratory control will permit new use of physiologic- and organ-based knowledge and complements studies of environmental and pharmacologic factors operating to produce respiratory disorders of sleep and of hypoventilation during wakefulness. Furthermore, risk factor identification and modification, if viewed within a molecular framework, will facilitate insight into the influence of development, growth, and exposure history of the expression of disease.

Specific Objectives. This communication is a report from a workshop during which experts in the fields of respiratory control, clinical disorders of respiratory control, genetic epidemiology, and molecular genetics reviewed and designed models for research in obstructive sleep apnea hypopnea syndrome (OSAHS) and sleep hypoventilation syndrome (SHS). The report is not intended to be a critical review of the state of current knowledge, but will indicate the range of appropriate opportunities to promote research and training on the molecular and genetic bases of disorders of respiratory control. A brief, annotated list of references that was made available to all committee members is given at the end of the report. These references are not intended to be comprehensive nor preclude critical or opposing viewpoints.

Introduction. Obstructive sleep apnea hypopnea syndrome (OSAHS) is a condition characterized by daytime symptoms of fatigue and excessive

from cardiovascular events, at least in some instances. Therefore, identification of genes found in people with OSAHS may be relevant to these putative risk factors and intersect with diseases, like diabetes, in which genetic factors may also play a role.

Risk factors thought to be in need of better definition as risk factors were the functional characteristics of the upper airway including its collapsibility and susceptibility to change during sleep. The problematic nature of the assessment and quantification of arousals and traits of sleepiness were recognized; however, assays relevant to epidemiologic (population-based) studies are needed. Finally, associations with other state-related disorders, like sudden infant death or apparent life threatening events of infancy, indicate the need to address developmental expression of traits relevant to the pathogenesis of adult disorders.

David Gozal led the presentation on SHS, and focused on focusing on Congenital Central Hypoventilation Syndrome. CCHS presents in infancy and childhood. Some 200 or so families currently have been identified in the United States. Familial clustering occurs but there is a high proportion of apparently sporadic cases. An essential trait of this syndrome is an absent CO₂ response during sleep; however, there seems to be a lack of integration of CO₂ responsiveness as with exercise these children may exhibit normal arterial CO₂ levels. Etiology is not known. Morbid outcomes includes failure to thrive, cardiopulmonary complications and death. Hirshprung's disease occurs in 14% of reported cases; but to date linkage to genes found with this disorder has been unrevealing. Anecdotal reports identify abnormalities in craniofacial features, of which there are no systematic studies. The essential features of the CHHS syndrome relate to a state-related lack of CO₂ responsiveness and a failure to maintain a constant CO₂ level during sleep and quiet wakefulness. In this manner CHHS is related to adult presentations of SHS, as acid-base balance is not maintained well during sleep even in the absence of sleep apnea.

Other attendees discussed the value of statistical approaches. In genetic epidemiology population studies are selected to exhibit sufficient power to detect the relative influence of inheritance and the environment on the distributions of traits relevant to OSAHS and SHS. This design focuses subsequent strategies for linkage or association studies in human populations. The consensus was that the current state on understanding in OSAHS, SHS, and CCHS was such that the next step is to develop a consistency among centers and studies in the definition of disease, clinical associations, and risk factors. Without such criteria, the outcome from gene studies would be difficult to assess.

Rodent studies were cited as examples of how to find significant gene loci or to study the effect of certain candidate genes on the intermediate physiologic systems, like respiratory control, obesity, craniofacial structures, and sleep itself. For instance, studies in the mouse and in the rat are underway to identify the mode of inheritance regulating tidal volume and frequency. Determining candidate markers would permit focused studies on sleep and cardiovascular interactions. Animal studies may be the only way to understand how cells from the neural crest develop and become the structural and functional elements involved in brainstem cardiorespiratory control in the adult mammal. Finally, the rarity of CCHS may elevate the importance of such models in any search for the molecular bases of respiratory control.

Another line of relevant research (that was surprising to clinicians) is the study of lower organisms. Of course, these organisms do not have OSAHS nor CHHS; however, there is enormous potential for studies of *Drosophila*, *C. elegans*, and zebrafish to dissect the molecular elements operating to

promote molecular and genetic approaches to the understanding of disease and disease-producing conditions. In Table 1 is a listing of some initiatives released in the past 18 months directly or indirectly related to neural control systems and cardiorespiratory control, in particular. Some of our research community have taken advantage of these initiatives; however, it is likely that colleagues, outside our discipline and in our respective academic centers, have also applied for these funds. Partnering with these other individuals who do not usually think of respiratory control as an important health issue is one way to start. It is likely that this line of research initiatives by the NIH and the NHLBI will proceed.

A second breakout group focused on the study of humans and produced the general model of strategic goals for gene finding in human populations. At the present time, it was considered premature to advocate a national initiative for gene finding. Rather, the focus should be on developing the tools for assay of phenotypes of interest that predict disease expression.

Initiatives needed to improve of the collection of human data included strategies to measure traits in large numbers of people, who then can be followed over time. The long term goal would be to track a quantitative (or semi-quantitative) measurement, like neck size, that could turn out to be predictive of disease onset or progression of disease. In addition, there would be the collection of qualitative and quantitative, complementary, but secondary characteristics. Two other points were discussed. First, a survey to be successful should be comprehensive enough to offer a hope of identifying distributions relating to affected or unaffected individuals. Second, the ability to collect this data in large numbers may be dependent upon community- and home-based observations as a first screen. Experience suggests that more people of all ethnic backgrounds participate more readily if data collection is brought to them rather than they go somewhere unfamiliar for study.

There is, moreover, a need to refine our measurement and understanding of traits that we currently hold as having promise in genetic epidemiologic studies. At the present time the apnea hypopnea index (AHI) or an equivalent measure such as the respiratory disturbance index (RDI) is the metric upon which many decisions are made, and one for which there is the most epidemiologic data. There is a need to dissect the components of respiratory events, perhaps even proposing an index comprised of several variables relevant to the disease state. These might include apnea length, total apnea time, arousal indices, or hypoxic history that create metrics for values that would disclose modal distributions or be amenable to multivariate analysis. Newer technology for the measurement of hypopneas or periods of high upper airway resistance may provide a greater range or a newer metric for events; however, issues of reproducibility and changes over time are important features to explore in any variable proposed as replacing AHI or RDI.

Another area of interest was that of tests during wakefulness that would predict the occurrence of sleep disordered breathing. Such measures might include ventilatory responsiveness (hypoxia, hypercapnia, and loading) or protocols looking at aspects of upper airway function. The collection of several features might allow a composite index for upper airway risk. A hope was expressed of the development of human assays that are akin to methacholine challenge to identify upper airway functional phenotypes of interest.

There was a highly speculative discussion of the potential use of markers to further stratify at risk individuals. This approach is used in diabetes and cardiovascular epidemiology. Potential biochemical and molecular markers might include those for diabetes (eg. glucose, insulin, etc.), cardiovascular diseases (eg. plasma homocysteine, folate, etc.), hypoxia (eg. uric acid

Building a Future. There is opportunity now with the growing compendium of information on gene function to do better physiologic studies and design studies that are directly relevant to human disease. Understanding and finding gene structures will rely heavily on bio-informatics, the use of model organisms and assumptions concerning the conservation of critical functions. Gene pathways and the "structural" elements of a molecular pathway can be efficiently studied in lower organisms, while integrated organ physiology, anatomic connections, and development of physiologic function are better studied in mammals. Therefore, there will be an interdependence among those who will study lower and higher organisms for understanding respiratory control.

The story of respiratory control will be complex. There will result the finding not only of one gene but many genes. Conceptual approaches must accept interactions and ask the appropriate questions at appropriate times. Investigators should be able to move from the autopsy table to the sleep laboratory to the critical care unit to model organisms and back again in order to reach a goal for early detection, better treatment, and prevention of the onset or progression of OHAHS, adult SHS, and CHHS.

Action items. The Assembly of Respiratory Neurobiology and Sleep will work with the ATS leadership and other professional organizations (American Physiologic Society and American College of Chest Physicians) to create opportunities for greater training in genetics for respiratory control and these disorders linked to respiration. One method might be to promote or even subsidize members to attend programs such as NHLBI Sponsored Programs for Molecular Genetics, currently held at Jackson Laboratory, Bar Harbor, Maine. Another is the development of workshops at annual meetings to elevate the level of competency and sophistication of the membership in the Human Genome Project. Seed money is needed to establish a knowledge system in the application of genomic information to the physiology of respiratory control and to clinical disease. The ATS and its leadership should take the lead in promoting this line of research to private and federal agencies.

The Assembly on Respiratory Neurobiology and Sleep should follow-up on the dissemination of this report by incorporating questions about it in subsequent member surveys. The committee co-chairs will also attempt to monitor the development of workshops and research programs and try to determine if these activities are the direct or indirect result of this process. The co-chairs also invite feedback on this method of disseminating conference reports.

Table 1: Some NIH Initiatives in the Past 18 Months (end date 4/99)	
HL-99-010:	Development Of Mouse Phenotypic Screens For Heart, Lung And Blood Diseases
HD-99-007:	Mouse Mutagenesis And Phenotyping: Developmental Defects
HL-99-013:	Rat Genome Database
HL-99-001:	Phenotypic Characterization Of Sleep In Mice
MH-99-012:	Neuroimaging Analyses As Correlates Of HIV/CNS Disease
MH-99-	Mouse Mutagenesis And Phenotyping: Nervous System And

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