

Role of Genetics in the Health Disparity of Premature Birth and Low Birth Weight Infants

**ROCKVILLE, MD
MAY 4, 2001**

Workshop Summary

WORKSHOP ORGANIZING SPONSOR:

National Institute of Child Health and Human Development, National Institutes of Health
U.S. Department of Health and Human Services

The statements, conclusions, and recommendations contained in this document reflect both individual and collective opinions of the symposium participants and are not intended to represent the official position of the U.S. Department of Health and Human Services, or the National Institutes of Health.

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NICHD WORKSHOP: The Role of Genetics in the Health Disparity of Premature Birth and Low Birth Weight Infants

PURPOSE: A racial and ethnic health disparity exists in the incidence of premature birth and low birth weight infants. The purpose of this workshop is to advise the NICHD in formulating a research agenda to examine the role of genetics in possibly underlying a part of this disparity. The objectives of the workshop are to review the research done in this area, identify important research gaps, and suggest various strategies to close these gaps. The themes and speakers of the workshop are listed in the agenda.

WHEN: May 4th, 2001

TIME: 9:00 am to 4:50 pm

WHERE: 5th Floor Conference Room, 6100 Executive Blvd, Rockville, Maryland

QUESTIONS: Call Mrs. April Mellinger (301-435-6903) or Dr. John Ilekis (301-435-6895)

AGENDA

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|-----------------------|---|
| 9:00-9:15 am | Welcome and Introduction
<i>Dr. John Ilekis, organizer, NICHD</i>
<i>Dr. Kenneth Ward, organizer and chairperson, University of Utah</i> |
| 9:15-10:00 am | Overview of the Problem
<i>Dr. Robert Goldenberg, University of Alabama</i> |
| 10:00-10:45 am | Strategies for Finding Disease Susceptibility Genes
<i>Dr. Dennis Drayna, NIDCD</i> |
| 10:45-11:00 am | Break |
| 11:00-11:45 am | Limitations of Race and Ethnic Associated Differences in Disease
<i>Moving Beyond Folk Taxonomies in Human Biodiversity Studies: Alternative Scientific Approaches.</i>
<i>Dr. Fatimah L. C. Jackson, University of Maryland</i> |
| 11:45-12:15 pm | Overview of the Genetics and Mechanisms of Premature Birth
<i>Dr. Kenneth Ward, University of Utah</i> |
| 12:15-1:00 pm | Lunch Break |
| 1:00-1:45 pm | Overview of the Biology of Fetal Growth and Intra-Uterine Growth Retardation
<i>Biological Mechanisms of Fetal Growth and IUGR Growth Standards, Definition and Biological Mechanisms of IUGR</i>
<i>Dr. Jorge Prada, University of Cincinnati</i> |
| 1:45-2:30 pm | Genetic Variation and its Relationship to Premature Birth
<i>Bacterial Vaginosis, Tumor Necrosis Factor-alpha and Spontaneous Preterm Deliver</i>
<i>Dr. George Macones, University of Pennsylvania</i> |
| 2:30-3:15 pm | <i>Molecular Epidemiologic Study of Preterm Delivery: Evidence of Gene-Environment Interactions in Diverse Populations</i>
<i>Dr. Xiaobin Wang, Boston University</i> |
| 3:15-3:30 pm | Break |

3:30-4:15 pm	Limitations of Race and Ethnic Associated Differences in Disease <i>Birth Outcomes, Socioeconomic Status and Health Disparities</i> <i>Dr. Richard David, University of Illinois</i>
4:15-4:20 pm	Break
4:20-4:50 pm	Speaker-Panel Discussion and Advice to NICHD

Abstracts

Introduction

Dr. John Ilekis, NICHD

A significant gap exists in the rate of low birth weight infants born to certain racial and ethnic groups compared to Caucasians. This gap is primarily due to differences in the incidence of premature birth. In fact, premature birth is the leading cause of neonatal mortality and morbidity in African-Americans. It is apparent that negative societal factors (i.e., low socioeconomic status, racism, poor or differential treatment in medical care) as well as negative behavioral factors (i.e., unprotected sex and tobacco/alcohol/drug use) play a major role in this health disparity. It is speculated that these factors alone contribute to at least 50 percent of the disparity. In addition, uterine infection is thought to play a significant role, at least in the case of African Americans, and is speculated to contribute an additional 30percent to the disparity. The remainder of the gap, or approximately 20 percent, is unexplained and may be due to hereditary or other unknown environmental factors.

It is unclear, however, how negative societal, behavioral, and other environmental factors alter gene expression or how different genetic backgrounds interact with these factors to increase a mother's susceptibility for preterm birth. Research in the area of gene-environmental interactions and their relationship to premature birth is evidently needed to better understand the pathophysiology behind the health disparity of premature birth.

Overview of the Problem

Dr. Robert Goldenberg, University of Alabama

Preterm birth in the United States occurs in 11percent of all births, with African American women having a rate of 17percent and white women 9percent. From 1970 to 1990, the preterm rate in African American women rose while it stayed relatively stable for white, Hispanic, Asian, and Native American women. Since 1990, the preterm birth rate for African American women has declined while it has risen slightly for white women. The very low birthweight rate (<1500g) generally followed the same patterns with recent <1500g rates in African American women of about 3percent, and in white women 1percent. Major risk factors for preterm birth include prior preterm birth, the earlier the prior preterm birth and the greater the number of prior preterm births, the higher the risk. Also, the earlier the prior preterm birth, the earlier the preterm births tend to occur in subsequent pregnancies. Maternal thinness measured by a body mass index <19.8 was a consistent strong risk factor for preterm birth. The predictive values for preterm birth of fetal fibronectin (fFN), vaginal ultrasound, and bacterial vaginosis were compared with traditional predictors. fFN, short cervix, and prior preterm birth were consistently the strongest predictors. The rates of infection with various sexually transmitted diseases by race were presented. African American women were significantly more likely to have each infection (bacterial vaginosis, syphilis, gonorrhea, chlamydia, etc.) than were white women, with these differences not generally explained by age of first intercourse, numbers of partners, etc. Peripartum infections such as chorioamnionitis and endometritis were also increased in African American women. The relationship between histologic chorioamnionitis, amniotic fluid infection of women in labor with intact membranes, and intramembrane infection in women delivered by C-section without membrane rupture all suggest that, at 1000g or <28 weeks, >80 percent of women have an intrauterine infection. The data also suggest that bacterial vaginosis is a precursor for the intrauterine infection, and that the intrauterine infection is often chronic with weeks to months elapsing between documentation of an inflammatory process and spontaneous preterm birth. Most women with intrauterine infection do not have fever, chills, pain, or an elevated white count, but instead manifest their infection with uterine contractions or by rupturing their membranes. Why African American women have so many more vaginal and intrauterine infections is one of the most important unanswered questions in obstetrics today.

Limitations of Race and Ethnic Associated Differences in Disease

Moving Beyond Folk Taxonomies in Human Biodiversity Studies: Alternative Scientific Approaches

Dr. Fatimah L. C. Jackson, University of Maryland

Recent insights from the Human Genome Project have confirmed the prevailing consensus in biological anthropology concerning contemporary human biodiversity. Humankind is but a single biological race, *Homo sapiens sapiens*. Population assessments at molecular and biochemical levels of evaluation as well as anthropometric studies indicate that there is tremendous genetic and phenotypic diversity and redundancy across the geographical range of modern humans.

All existing variation therefore occurs at the sub-species taxonomic level. This fact strongly implies that scientists must exercise more, rather than less, care when looking for group-level differences in disease susceptibility or expression. While there is comfort in these similarities, the species' evolutionary strength is in its differences. The meaningful stratification of this diversity requires greater attention to nuance, anthropological detail, and historical context than traditional broad-based groupings ever permitted.

This presentation critiques the limitations of 19th and 20th century perspectives on human variability and suggests alternative scientific approaches through ethnogenetic substructuring and sampling regimes. Ethnogenetic sampling is a biocultural strategy to identify local variants of interest in biomedical or ancestral reconstructions. Preliminary analysis of this approach suggests that it can provide important insight into the true magnitude of biodiversity and its origins among various socially and geographically defined groups. Only when accurate, interdisciplinary perspectives are integrated in the assessment of modern human differences and similarities can scientists begin to understand the interrelationship of genes, environment, and the expression of complex phenotypes such as prematurity and low birth weight.

Overview of the Genetics and Mechanisms of Preterm Birth

Dr. Kenneth Ward, University of Utah School of Medicine

Genetic factors involved in human birth weight have been studied extensively. It is estimated that 40 percent of birth weight variance is due to genetic factors, and the remaining 60 percent is due to environmental factors. The heritability of low birth weight and macrosomia is greater than the heritability of average weights.

Premature labor has a tendency to recur in subsequent pregnancies and there is anecdotal evidence of familial factors, however, the genetics of premature delivery have received little systematic study. A history of a prior preterm delivery (PTD) is a major risk factor for PTD in subsequent pregnancies. Having a mother or a sister who delivered preterm is a major risk factor as well.

Our analysis of PTD in Utah, where extensive genealogy records are available, suggests a familial tendency. Birth certificates from two successive generations were linked and compared, revealing that the tendency to deliver a preterm infant is highly heritable. Utah has a relatively low rate of PTD due to infections or drug abuse; most cases of preterm labor are idiopathic. For the past three years, every patient on the Obstetric Service at the University of Utah Hospital who delivered prior to 35 weeks of gestation has completed a questionnaire about her family history regarding preterm delivery. Forty two percent of patients reported that their mother had one or more PTDs. Because of the large average family size in Utah, patients who delivered preterm had an average of 1.2 sisters who are also parous, and many have also delivered preterm. Through this effort we have already identified over 90 sister pairs and several large families with an apparent genetic predisposition to PTD.

There are well-described racial differences in the rate and outcome of PTD, even when other contributing etiologic-factors are controlled for. Self-described race has little formal genetic meaning. Many known environmental triggers assort by race as well, and there are likely to be unknown and understudied factors which contribute to this disparity

Preterm labor is a heterogeneous disorder. Multiple pathways are involved and each pathway will have genetic and environmental factors that play a role. There are likely to be mutations that affect the uterine clock, myometrial automaticity, cervical length, etc. The disease genes will usually be contributory rather than causative, but rare families with a profound mutation should be sought because they may elucidate a critical Achilles heel in these physiologic pathways

Others and we are using the proven technique of positional cloning (the isolation of a gene solely on the basis of its chromosomal location, without regard to its biochemical function) to investigate genetic factors in PTD. "Candidate genes" are being screened first, including the genes for: oxytocin, oxytocin receptor, cyclo-oxygenase, nitric oxide synthetase, interleukin-1 receptor, et cetera. The discovery of a gene predisposing to PTD would be a major breakthrough for future research into biology, prediction, and therapy of preterm labor.

Overview of the Biology of Fetal Growth and Intra-Uterine Growth Retardation (IUGR)

Biological Mechanisms of Fetal Growth and IUGR

Dr. Jorge Prada, University of Cincinnati

Regulation of growth of the fetus begins before pregnancy. Maternal and paternal genetic variations are likely to influence fetal growth. There are differences in growth curves in different geographic regions and among different racial groups in the United States. However, it is exceedingly difficult to separate the influence of environmental factors from true genetic differences. The antenatal diagnosis of IUGR is based on limited understanding of the stages of fetal growth. Any deprivation or insult occurring during pregnancy may interfere with intrauterine growth, thus preventing the fetus from attaining its original growth potential. The causes are multiple, comprising many different factors: biomedical mechanisms, hormonal regulation, nutritional and placental function, and the maternal environment. These factors may involve the fetus, the placenta, the mother, or a combination of the three. The biological mechanisms of IUGR are not likely to be independent causative elements but rather important mediating factors of a pathologic process set in motion by other insults.

Genetic Variation and its Relationship to Premature Birth

Bacterial Vaginosis, Tumor Necrosis Factor-alpha and Spontaneous Preterm Deliver

Dr. George Macones, University of Pennsylvania

Background: The rarer of two alleles of a polymorphism in the promoter of the tumor necrosis factor alpha (*TNFA*) gene is associated with spontaneous preterm birth following preterm premature rupture of the fetal membranes. The aim of this study was to assess whether the presence of symptomatic bacterial vaginosis amplifies the risk of spontaneous preterm birth in those with a "susceptible" *TNFA* genotype.

Methods: A case-control study was performed at the University of Pennsylvania. Cases (n=50) were defined as women who delivered prior to 37 weeks secondary to ruptured membranes or preterm labor, while controls (n=200) were defined as women who delivered after 37 weeks. DNA was collected from maternal blood and analyzed for the *TNFA* genotype. Information on symptomatic bacterial vaginosis and other risk factors for preterm birth was obtained by review of the antenatal record. Analyses consisted of bivariate and stratified analysis. Multiple logistic regression was also used to test the interaction between bacterial vaginosis, the *TNFA* genotype, and preterm birth.

Findings: Maternal carriers of the rarer allele (*TNF-2*) were at a significantly increased risk of spontaneous preterm birth (OR=2.4, 95percent CI 1.3-4.5). The association between *TNF-2* and preterm birth was modified by the

presence of bacterial vaginosis, such that those with a “susceptible” genotype and bacterial vaginosis had an increased odds of preterm birth compared to those who did not (adjusted interaction OR=9.2, 95percent CI 1.1-55.1).

Interpretation: This study provides the first evidence that an interaction between genetic susceptibilities (i.e., *TNF-2* carriers) and environmental factors (i.e., bacterial vaginosis) is associated with an increased risk of spontaneous preterm birth.

Genetic Variation and its Relationship to Premature Birth

Molecular Epidemiologic Study of Preterm Delivery: Evidence of Gene-Environment

Interactions in Diverse Population

Dr. Xiaobin Wang, Boston Hospital

While the causes of preterm delivery remain unclear, preterm delivery appears to be a highly complex entity determined by multiple environmental and genetic factors, as well as gene-environment interactions. Most previous studies have focused on socio-environmental or clinical variables. The role of genetic susceptibility and gene-environment interactions in relation to preterm delivery is largely unexplored. This presentation will summarize findings of gene-environment interactions on low birthweight or preterm delivery from ongoing molecular epidemiologic studies of preterm delivery in both Chinese and U.S. populations, specifically, interactions between: (1) metabolic genes and benzene exposure; (2) metabolic genes and cigarette smoking; and (3) corticotrophin releasing hormone (CRH) gene and maternal perceived stress. In addition, important methodological issues in this research field will be discussed. These data have provided a consistent evidence of gene-environment interactions in diverse populations. However, more studies are needed and multidisciplinary collaborations are required in order to jointly and comprehensively assess the role of socio-environmental factors, genetic factors, and gene-environment interactions in preterm disparity among populations with marked differences in social status and experiences.

Limitations of Race and Ethnic Associated Differences in Disease

Birth Outcomes, Socioeconomic Status and Health Disparities

Dr. Richard David, University of Illinois

Two features characterize infant mortality in the United States: (1) The rate is high for a rich, industrialized country; and (2) Mortality in the first year — indeed, mortality at all ages — is strikingly worse for African Americans compared to whites. Moreover, the situation is deteriorating. Both the international standing of U.S. rates and the nation’s African American-white disparity has been worsening in parallel for over three decades. Survival of both white and African American infants is closely linked to racial disparities in survival. Understanding and eliminating these disparities has rightly been identified as essential to improving health outcomes for all Americans.

During the 1970s and 1980s researchers tried to explain the African American-white gap in infant outcomes by studying the socioeconomic gap. Epidemiologists reasoned that the different rates of poverty in different ethnic groups would explain the differences in prematurity and death. These attempts failed. African American-white differences persisted even when groups of college graduates were compared. This finding led some to speculate about “genetic” differences between the social groups called “races” while others began the search for social mechanisms beyond the traditional risk factors of income and education.

We have carried out two types of work over the past ten years to address the persistent African American-white gap in low birth weight, prematurity, and infant death rate. The first is to challenge the biological concept of race as it applies to birth weight. The second approach has been to explore novel risk factors for low birth weight and prematurity. These risk factors attempt to capture aspects of the multifaceted and multi-layered phenomenon known as “racism.”

Most anthropologists have now abandoned the biologic-genetic concept of race, but the concept still holds sway in medicine and epidemiology. A 1993 study of 1,149 bi-racial babies showed that the effect of the parents' race on the birth weight of their offspring depended on which parent was African American. Bi-racial infants whose fathers were African American had no birth weight disadvantage compared to infants with two white parents, once age, education and income were taken into account. A birth weight effect persisted after socioeconomic status (SES) adjustment for infants of African American mothers, however. This maternal-specific race effect suggests social or environmental mechanisms working through the mother. Another study in 1997 tested the notion of a genetic race effect on birth weight using a population of women born in West Africa but giving birth in the United States. The genetic theory would predict a worse birth weight outcome for these women compared to African American women, who trace 25 percent of their ancestry to European forebears. The findings were the opposite: African-born African American women had babies whose birth weight distribution was close to that of white women, some 300 grams heavier than African American infants. "Genetic race" does not fit with these results.

Our work on novel risk factors that might underlie African American-white disparities has so far focused at two levels: the neighborhood and the interpersonal. Although small sample sizes, primitive measurement instruments, and other problems limit this early work, we have nevertheless made some interesting observations. In a 1997 study using vital records and police crime data, we found that African American infants from neighborhoods with high rates of violent crime had a higher rate of intrauterine growth retardation than African American infants from less violent areas, even after controlling for income. We found supportive evidence for such neighborhood effects in a study published the following year using a different approach. In this 1998 study, we employed a case-control design, interviewing African American women who gave birth prematurely and comparing their responses to those of African American women who had normal sized infants. Despite similar sociodemographic characteristics, women who rated their neighborhoods unfavorably in terms of safety, cleanliness, school quality, and several other factors were 1.7 to 3.2 times more likely to deliver infants weighing less than 1.5 kg compared to women who rated their neighborhoods more favorably. (All women in these studies were African Americans.)

Using a similar case-control design, we found that African American women experiencing three or more stressful life events in pregnancy have 3.1 times the likelihood of very low birth weight. This result is similar to previously published studies conducted in mostly white populations by other investigators. In our most recent study, we focused on a type of social stress in pregnancy, which is specific to minority women: racial discrimination. Using a questionnaire administered by trained African American interviewers, we asked African American women about perceived discrimination in each of five domains (at school, getting service at a restaurant, in housing, etc.). Although the effect was not uniform, among high-risk women the experience of discrimination was associated with a 4.4-times greater risk of very low birth weight.

Racial disparities in newborn outcome have not disappeared, but rather have increased over recent decades, even as class differences in wealth have grown and overall U.S. health indices have deteriorated by international standards. We speculate that these trends are causally related. The underlying mechanisms of race and class disparity should be sought in political economy. Their elimination will probably require profound social change as well as a fundamental rethinking of outmoded ideas like the biological-genetic concept of race.