HOW GENETIC AND SOCIAL INFLUENCES DRIVE POOR BIRTH OUTCOMES AND DISPARITIES: CURRENT DEBATES

Monday, May 21
10:20 AM - 11:50 AM

#prematuritycollab
Addressing Health Equity in PTB Research: Is racism a missing piece of the puzzle?

March of Dimes Prematurity Prevention Summit: Building a Birth Equity Movement
Arlington, Virginia
May 21, 2018

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What is health equity?

Health equity means that everyone has a fair and just opportunity to be as healthy as possible. This requires removing obstacles to health such as poverty, discrimination, and their consequences, including powerlessness and lack of access to good jobs with fair pay, quality education and housing, safe environments, and health care.

For the purposes of measurement, health equity means reducing and ultimately eliminating disparities in health and its determinants that adversely affect excluded or marginalized groups.
Persistent racial disparities in preterm birth (PTB): An unequal start in life

- PTB strongly predicts infant mortality, childhood disability & adult chronic disease
- African Americans (Blacks) have persistently had > 1.5 times the PTB rate of European Americans (Whites)
- Causes largely unknown
  - PTB vs PTB disparities
The causes of PTB and PTB disparities are unknown

Not explained by:
• Standard prenatal care
• Tobacco, alcohol, drugs
• Current income or education

Some researchers suspect:
• Infections
• Elective C-sections
• Environmental toxins
• Nutrition
• Neighborhood conditions
• Stress, social support
• Lifelong experiences, especially in childhood
• Genetic differences or gene-environment interactions
Evidence suggests social causes are important in the Black-White disparity in PTB

- Black immigrants from Africa have birth outcomes similar to Whites’
  - But worse BW outcomes among African immigrants’ daughters
- Neighborhood features often matter
- Poor White and Black women have similar PTB rates (Racial disparity greatest among higher SES women)
- Stress seems important, including potentially in infections
- Black women’s lower PTB rates in Centering Pregnancy
- Black women who often worried about being treated unfairly based on race were twice as likely to have PTB
  - Racial disparity non-significant after adjusting for worrying often about racism
Racial segregation and environmental injustice could increase many African-Americans’ PTB risks

- Pollution, toxins, crime
- Poor schools
- Low economic opportunity
- Stressful, unhealthy neighborhoods
- Despair
- Social isolation vs support
- **Racial segregation tracks Blacks into poorer neighborhoods than Whites of similar income**
Stress could be important, based on current neuroscience

- Stress could result from financial hardship and from psychological effects of racism
- Studies have identified biological mechanisms through which chronic stress can damage health
  - Inflammation and immune function appear important
  - Can trigger labor
  - Stressful experiences may have epigenetic effects
The stress → PTB link: Biologically plausible?

**STRESSOR**

- Hypothalamus
  - CRH
- Pituitary Gland
  - ACTH
- Adrenal Glands
  - CORTISOL

**DAMAGE TO MULTIPLE ORGANS & SYSTEMS**
- Inflammation, immune suppression, chronic disease, premature aging
Does racism-related stress increase African-American women’s risk of PTB?

- Chronic racism-related stress could lead to chronic disease and PTB through neuroendocrine and immune mechanisms
- Earlier qualitative study
- Women reported overt, subtle, and ambiguous incidents
- Constant vigilance
- All could be stressful, even if not dramatic
- Higher-SES women reported more discrimination & vigilance
Does chronic worry about racism contribute to PTB disparities?

• CA. Maternal & Infant Health Assessment, annual statewide survey by CA Health Dept/UCSF
• US-born, non-Latino Black (2,201) or White (8,122) women who gave birth in 2011-14
• “…how often have you worried that you might be treated or viewed unfairly because of your race or ethnic group?”
  ▪ Often= very or somewhat often
  ▪ 36.9 (32.9-40.9)% of Black & 5.5 (4.5-6.5)% of White women reported worrying often

Higher-income/education Black women were most likely to worry often about racism.

**Income**
- ≤100% FPL: 31.8%
- 101-200% FPL: 44.3%
- >200% FPL: 49.7%

**Education**
- <High school: 33.8%
- High school/GED: 24.7%
- Some college: 40.5%
- College graduate: 47.5%
Worrying often about racism was associated with PTB

- PTB was twice (PR 2.00, 1.33-3.01) as likely among Black women who often worried about racism as those who did not
- Even after adjusting for multiple socioeconomic/demographic, psychosocial/behavioral, & medical characteristics:
  - Income, education, age, parity, marital status, neighborhood poverty
  - Smoking, binge drinking, unintended pregnancy; pregnancy stressors and depressive symptoms
  - Pre-pregnancy health status, diabetes, HTN or underweight; delayed prenatal care; pregnancy weight gain
- Black-White disparity in PTB (PR 1.59, 1.21-2.09) was nonsignificant (PR 1.30, 0.93-1.81) after adjusting for chronic worry about racism and appeared further attenuated (PR 1.17, 0.85-1.63) after adding the covariates
Not definitive, but warrants further study

- Only one question, not formally validated. Almost all information self-reported
- Racism-related stress across the life course is plausible biologically as a key risk factor for PTB disparities
- May explain why higher income or education doesn’t seem to confer the same advantage on Black women as on White women
- Difficult to explain the findings with underlying genetic difference although gene-environment interaction cannot be ruled out.
  - Implications: Genes are not destiny. “Genes load the gun; the environment pulls the trigger” (J. Stern)
- Equity and good science call for more investment in studying the role of social factors, including stress across the life course, in PTB
Unmeasured socioeconomic differences are plausibly very important in PTB disparities

The legacy of once-legal discrimination: Structural racism →
Lower levels of income, wealth, education, occupation; more incarceration

Because of racism, at a given income or educational level, African Americans:
- Have far less wealth
- Live in under-resourced, often unhealthier neighborhoods
- More hardship with fewer resources to cope
- Impact on families
- Since childhood
- Rarely measured but studies often conclude a racial difference is genetic if it persists after “control for SES”
- “Race” often captures unmeasured socioeconomic factors
“Race” – or Racism?

- Racism → low SES → exposures/hardships → health damage
- And racism → more direct psychological effects → health damage
- Relevant factors rarely measured
- “Race” variable picks up unmeasured experiences of racism across the lifecourse/generations

Image: http://www.empowermagazine.com/how-racism-affects-your-health
paula.braveman@ucsf.edu
How Social Determinants Drive Disparities in Preterm Birth

James W. Collins, Jr
U.S. Birth Outcomes Vary by Maternal Race and Country of Birth

- AA (compared to White) women have a 1.6-fold greater preterm birth (< 37wks, PTB) rate.
- Foreign-born Black women who immigrate to the U.S. have a PTB rate more similar to that of US-born White than US-born Black women.
- The favorable birth outcome quickly (i.e. one generation) disappears among the US-born descendants of foreign-born Black women.

(David and Collins, NEJM, 1997; Pallotto et al; AJE, 2000; Collins et al AJE, 2002; Deal and Collins, Ethn Dis, 2014)
The Maternal Age Related Patterns of PTB Differ by Race, Cook County, IL

(Love et al, AJE, 2010)
Neighborhood Poverty, Racial Discrimination, Job Strain, and Partner’s Low Socioeconomic Position: a Life-Course Conceptual Model
Neighborhood Poverty
Lifetime Neighborhood Experiences in Chicago: White and Black

- **Lifelong High-income**: 84.0% Whites, 2.3% African-Americans
- **High-income/Low-income**: 7.4% Whites, 12.1% African-Americans
- **Low-income/Low-income**: 6.6% Whites, 7.3% African-Americans
- **Lifelong Low-income**: 2.1% Whites, 78.3% African-Americans

**Lifelong Residential Environment**

- **Percent**
- **Whites**
- **African-Americans**
Impoverished-Born AA Women’s Upward Economic Mobility is Associated with Lower PTB Rates
(Collins et al AJPH, 2011)
Impoverished-Born AA Women’s Upward Economic Mobility is Associated with Lower PTB Rates Independent of Education

Maternal Upward Economic Mobility

- None
- Low
- Modest
- High

PTB rates (per 100 livebirths)

- \( \leq 12 \text{ yrs} * \)
- \( > 12 \text{ yrs} * \)
Impoverished-Born AA Women’s Upward Economic Mobility is Associated with Lower PTB Rates Independent of Prenatal Care

Maternal Upward Economic Mobility

PTB rates (per 100 livebirths)

- None
- Low
- Modest
- High

Inadequate PC*

Adequate PC*
Upward Economic Mobility from Early-Life Impoverishment is **NOT** Associated with Lower PTB Rates Among Former LBW AA Mothers

*(Collins et al AJPH, 2011)*
Downward Economic Mobility is Associated With Increased PTB Rates Among Affluent-Born White Women

(Collins et al, MCHJ, 2015)
Racism
AA WOMEN’S LIFETIME EXPOSURE TO INTERPERSONAL RACISM AND BIRTH OUTCOME

(Collins et al, AJPH, 2004)
• Unadjusted and adjusted OR of preterm-VLBW for maternal lifetime exposure to interpersonal racial discrimination in 1 or more domains were 1.9 (1.2-3.1) and 2.3 (1.1-3.6), respectively.

• Unadjusted and adjusted OR of preterm-VLBW for maternal lifetime exposure to interpersonal racial discrimination in 3 or more domains were 2.7 (1.3-5.4) and 2.6 (1.2-5.3), respectively.
Worry About Racial Discrimination:
A Missing Piece of Black-White Disparities in PTB?

(Braveman et al, Plos One, 2017)

- 37% of AA vs 6% of White women reported chronic worry about racial discrimination.
- Chronic worry about racial discrimination was associated with PTB among AA: adjusted RR = 2.0 (1.2-3.0).
- The racial disparity in PTB was attenuated and became non-significant when adjusted for chronic worry: RR = 1.6 (1.2-2.1) and 1.3 (0.9-1.8), respectively.
Institutional Racism

“Redlining” is the practice of denying or charging more for services, such as banking, to residents in often racially-determined areas. The term refers to the practice of marking a red line on a map to delineate the area where banks would not invest.
Redlining

• 1999-2004 Home Mortgage Disclosure Act (HMDA) data: created residential redlining indices for census tracts in Philadelphia; appended to a relatively small pregnancy cohort (n=3,462) sample (Mendez et al, Public Health Reports, 2011)
  – African Americans were twice as likely to be denied a mortgage loan compared with white applicants independent of annual income, loan amount, and gender; they were more likely to live in redlined areas
  – Redlining was associated with residential segregation
AA PTB Rates By Redlining in Chicago
(PAS, 2016)

PTB Rates (per 100 live births)

Redlining Index Odds Ratio

- <1: 17.5, n = 12,482
- 1-1.5: 18.3, n = 12,564
- 1.5-2: 19, n = 7,564
- 2-2.5: 18.5, n = 4,109
- 2.5-3: 19, n = 1,568
- 3-3.5: 15, n = 301
- 3.5-4: 20.7, n = 140
- >4: 20.8, n = 96
Job Strain
Job Stresses in the Work Place

- Quebec women employed in positions characterized by high levels of job strain (high demand, low control) experienced about twice the risk of preterm birth (Croteau, AJE, 2007).

  - Preterm birth was significantly associated with jobs that allowed little control for the employee.
AFRICAN-AMERICAN WOMEN’S CHRONIC EXPOSURE TO INTERPERSONAL RACISM IN THE WORKPLACE AND PTB
(Collins et al, AJPH, 2004)

• Ten additional questions about racism in the work place.
• Responses were dichotomized after data collection into none ("none” or “less than once/ year”) or regularly (chronic) (“few times/year”, “few times/month”, “at least once/week”, and “nearly everyday”).
AFRICAN-AMERICAN WOMEN’S CHRONIC EXPOSURE TO INTERPERSONAL RACISM IN THE WORKPLACE AND PTB

(Collins et al, AJPH, 2004)

• “You are watched more closely than others because of your race”. OR=2.3 (0.8-6.1)
• “Whites often assume that you work in a lower class job than you do and treat you as such”. OR=2.3 (1.0-5.1)
• “You are treated with less dignity and respect than you would be if you were white”. OR=2.0 (0.8-4.3)
AFRICAN-AMERICAN WOMEN’S CHRONIC EXPOSURE TO INTERPERSONAL RACISM IN THE WORKPLACE AND PTB

(Collins et al, AJPH, 2004)
Fathers
The Excess PTB Rate for U.S.-born Black Women: Fathers Matter!
(DeSisto et al, Annals of Epi 2018)

- U.S.-born black vs. foreign-born black preterm birth disparity
- U.S.-born black vs. U.S.-born white preterm birth disparity

<table>
<thead>
<tr>
<th>Disparity Type</th>
<th>Unexplained</th>
<th>Other Variables</th>
<th>Maternal Education</th>
<th>Paternal Involvement</th>
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<tbody>
<tr>
<td>U.S.-born black vs. foreign-born black</td>
<td>0.28</td>
<td>0.19</td>
<td>0.41</td>
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<tr>
<td>U.S.-born black vs. U.S.-born white</td>
<td>0.19</td>
<td>0.43</td>
<td>0.52</td>
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</table>
Father’s Socioeconomic Position is Associated with LBW Rates:
(Collins et al, MCHJ, 2016)
AA Father’s Lifelong SEP is Associated with LBW Rates Among Married Parents
(Collins et al, 2016)
AA Father’s Lifelong SEP is Associated with LBW Rates Independent of Maternal Education

(Collins et al, MCHJ, 2016)
Father’s SEP and PTB Rates

(SPERS, 2017)

Lifelong Low

Lifelong High

0% 2% 4% 6% 8% 10% 12% 14%

Preterm birth rate

13.0%

9.1%

3.9%

6.0%

4.7%

1.4%

Late Preterm (34 to 36 weeks)

Early Preterm (< 34 weeks)
Adverse Environmental conditions

Social policy

Poverty
Limited Access to Care
Under-Education

Racism

Weathering
Unemployment
Paternal Low SEP

Stress

Preterm Birth

Bad Housing
Bad Neighborhoods

Lower Class Status
Job Strain
Poor Working Conditions

Lack of access to good Nutrition

Adverse Environmental conditions

Adapted from A. R. James
Improving Pregnancy & Birth Outcomes

Go Ecological

Begin to address the social and economic inequities that are the root cause of health disparities
INCORPORATING HEALTH EQUITY IN THE BASIC SCIENCE RESEARCH AGENDA

DAVID K STEVENSON

Department of Pediatrics
Stanford University School of Medicine
Stanford, CA
Disclosure Statement

I have nothing to disclose...
Why are black mothers and babies in the United States dying at more than double the rate of white mothers and babies? The answer has everything to do with the lived experience of being a black woman in America.

By Linda Villarosa
Although a person’s capacity for gene expression is critical to the development of a particular phenotype (*normal* or *pathologic*), demographic and psychosocial factors are equally critical and often the most tractable determinants of health disparities.

Interventions, which address demographic and psychosocial factors of health, offer powerful ways to improve personal and public health.
UNDERSTANDING DISPARITIES FROM THE PERSPECTIVE OF BASIC SCIENCE RESEARCH

• All aspects of the human condition have genetic and epigenetic (biologic) determinants.
• All aspects of the human condition have environmental (e.g., physical, demographic or psychosocial) determinants.
• A particular human phenotype is the expression of interactions between the genome and the exposome.
Understanding Disparities From The Perspective Of Basic Science Research

- It is a mistake to categorize a particular condition as genetic or environmental in origin.
  - Scurvy (L-gulonolactone deficiency) is often described simply as an environmental condition.
  - Phenylketonuria (phenylalanine hydroxylase deficiency) is often described simply as a genetic condition.
  - Preterm birth?
RISK FACTORS

BIOMARKERS (PROTEINS & OTHER MOLECULES)

GENES AND THEIR TRANSCRIPTS

CELL SIGNALING BEHAVIOR
AN INTEGRATED APPROACH FOR A SYSTEMS WIDE ANALYSIS OF TERM AND PRETERM PREGNANCIES

- Single Cell Immune Profiles (CyTOF)
- Cytokine Profiles
- Demographic Profiles
- Psychosocial Profiles
- Genomic Profiles
- Cell-free RNA Profiles
- Microbiome Profiles
INTEGRATIVE PERSONAL OMICS PROFILING

- Genome
- Transcriptome
- Epigenome
- Microbiome
- Proteome / Metabolome
- Immunome
- Exposome
IS IT POSSIBLE TO NON-INVASIVELY MONITOR THE DEVELOPMENTAL GENE EXPRESSION PROGRAM OF A HUMAN FETUS?
UTILITY OF CELL-FREE NUCLEIC ACIDS
435 Genes Display Temporal Changes Across Gestation

Normalized Expression

P-value < 0.02

Early-Expressed Genes (37)
Up-regulated Genes (108)
Down-regulated Genes (290)
Identified 40 Preterm Candidate Markers

P-value < 0.001
Temporal Changes Of Immune Genes

Normalized Expression

P-value < 0.02
Temporal Changes of Immune Genes

Normalized Expression

P-value < 0.02

S100A8 - regulation of inflammatory and immune response

Samples

Genes
Temporal Changes of Immune Genes

Normalized Expression

P-value < 0.02

S100A8 - regulation of inflammatory and immune response

NFATC2 - nuclear factor of activated T cells

Samples

Genes
THE IMMUNE BALANCE OF PREGNANCY: NATURE'S MEASUREMENT OF TIME DURING GESTATION

Tolerance/Immunosuppression

- Tregs
- Th2
- Dendritic Cells
- CD16+ NK cells
- Macrophages (M2)
- CD56+ NK cells
- B Cells
- Th17

Rejection/Inflammation

- Th1
- Neutrophils
- CD16+ NK cells
- Macrophages (M1)

Adrian Erlebacher Ann Rev Imm 2014
Mor, G. Ann N Y Acad Sci. 2011
Roberto Romero, Science, 2014
SINGLE CELL IMMUNE PROFILING OF PREGNANCY
CyTOF: Mass Cytometry by Time Of Flight Mass Spectrometry

1- Precise phenotyping of individual immune cells
2- Simultaneous interrogation of intracellular responses

Bendall, S. Simonds, E Science 2011
Validation Of 25 “Surface” Markers For The Analysis Of Pregnancy-induced Changes In Immune Cell Distribution Across The Entire Immune System
Validation of 12 “Functional” Markers for the Analysis of Pregnancy-Induced Changes in Immune Cell Function Across the Entire Immune System
SINGLE CELL IMMUNE PROFILING OF PREGNANCY

A. Training cohort (n = 18)
Validation cohort (n = 10)

Trimesters
T1 T2 T3 PP

B. CyTOF

C. Data categories (feature numbers)
SINGLE CELL IMMUNE PROFILING OF PREGNANCY

A. Training cohort (n = 18)

Validation cohort (n = 10)

Delivery

Trimesters

T1 T2 T3 PP

B. CyTOF

C. Data categories (feature numbers)

Gestational Weeks

Immune clock

Gestational Weeks

Trimesters

10 15 20 25 30 35
SINGLE CELL IMMUNE PROFILING OF PREGNANCY

A. Training cohort 
(n = 18) 

Validation cohort 
(n = 10) 

Trimesters 
T1 T2 T3 PP 

Delivery 

C. Data categories (feature numbers) 

B. CyTOF 

Gestational Weeks 

Trimesters 

Immune clock 

Gestational Weeks
**Single Cell Immune Profiling Of Pregnancy**

![Graph showing signatures of pregnancy over trimesters and term](Image)
SINGLE CELL IMMUNE PROFILING OF PREGNANCY

SIGNATURES OF PREGNANCY

TERM

PRETERM

INDIVIDUALS

AGGREGATE

TRIMESTER 1

TRIMESTER 2

TRIMESTER 3

POSTPARTUM
Preterm Birth Disparity: Ancestry as a Record of Gene-Environment Interactions
The progesterone receptor (PGR) plays a central role in maintaining pregnancy and is significantly associated with medical conditions, such as preterm birth.

There is substantial population differentiation at the PGR locus driven by natural selection.
Gestational Changes In The Progesterone Receptor Among Human Populations Through Natural Selection

• Derived alleles in the PGR locus common in East Asians are associated with a reduction in early spontaneous preterm birth and medically induced preterm birth risk (preeclampsia), suggesting positive selection that conferred an advantage to the human lineage.

• In the European population, the PGR locus was highly diversified by balancing selection which could reflect the fact that increased polymorphisms in the PGR locus were associated with immune adaptations when migrating to the European continent.

• East Asian specific alleles are at low frequencies in other populations, such as the SNP RS11224580.
DISTRIBUTION OF EAST ASIAN SPECIFIC PGR Derived Allele (RS1 1224580)
Given the different patterns observed in the African and European populations, the positive selection in East Asian populations likely occurred after the population split between Europeans and Asians.

Remodeling the PGR locus was only advantageous in East Asians for local adaptation (*positive selection*), but was deleterious in other populations (*negative selection*).
THE BOSTON BIRTH COHORT (AFRICAN AMERICANS)

86 high-frequency derived alleles (HD-SNP s)

sPTB
n=461

sPTB <32wks
n=115

mPTB
n=237

Controls
n=1,035

East Asian alleles increase early sPTB risk in African Americans

Common alleles decrease early sPTB and mPTB

GWAS from Xiaobin Wang, JHU
Gestational Changes In The Progesterone Receptor Among Human Populations Through Natural Selection

• The genotype only matters in an environmental context and how it matters is reflected in the phenotype, in this case preterm birth.

• Modern transportation, demographic, and psychosocial stressors have made gene-environment mismatches more prevalent.
What is normal for one population may not be normal for another—or conversely, what is pathologic for one population may not be pathologic for another.
VAGINAL MICROBIOTA OVER TIME

n = 40 subjects (29 term; 11 preterm), 996 samples

PC1 (32%)

Term Birth: n=29 subjects

Preterm Birth: n=11 subjects; GAD range 22-36 wks

Gestational Day

Postpartum Day

Time
Community State Type (CST) IV was found more frequently in women who delivered preterm.
CST IV exhibited a dose-response relationship w/ PB

Fraction of Vaginal Samples That Were CST IV

An increase in the proportion of time points that were in the diverse state correlated with a lower GA at delivery
Ravel et al. (2011) Proc Natl Acad Sci USA. 108:4680
• An intervention of high potential biologic efficacy may impact one population differently than another depending upon non-genetic or environmental determinants.

• What might be expected to diminish disparity can sometimes exacerbate it.
ALPHA DIVERSITY OF VAGINAL COMMUNITIES PRE- AND POST-DELIVERY

(n=22 subjects with ≥1 post-delivery sample)
# Relative Risk and Population Burden Both Matter

**California 2007-10**

<table>
<thead>
<tr>
<th>IPI Months</th>
<th>ALL PTB 20–36</th>
<th>sPTB 20–36</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>54,14 / 54,083 = 10.0%</td>
<td>40,02 / 52,671 = 7.6%</td>
</tr>
<tr>
<td>6 – 11</td>
<td>7,78 / 113,057 = 6.9%</td>
<td>5,415 / 110,691 = 4.9%</td>
</tr>
<tr>
<td>18 – 23</td>
<td>62,36 / 110,229 = 5.7%</td>
<td>54,64 / 109,457 = 5.0%</td>
</tr>
</tbody>
</table>

>13,000 babies born per year in California with IPI < 6 mos
Understanding Disparities From The Perspective Of Basic Science Research

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- All aspects of the human condition have environmental (e.g., physical, demographic or psychosocial) determinants.
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By Linda Villarosa
Placing the Genetics of Pre-Term Birth in Context

Wylie Burke MD PhD
Department of Bioethics and Humanities
University of Washington
Seattle, WA
Evidence for genetic contribution to PTB

Higher likelihood of PTB for women who:
- Were born pre-term themselves
- Have a family history of PTB
- Have had prior PTB

Twin and family studies suggest heritability of 17-40%

Monangi et al 2015 Seminars Perinatol
Dolan 2010 Mt Sinal J Med
Genes/pathways potentially associated with PTB

- No evidence of major gene effects
- No definitive findings – but preliminary evidence supports potential involvement of pathways involving:
  - Metabolism; endocrine processes; inflammatory and stress responses; collagen synthesis; coagulation

One study used genome-wide analysis to identify & replicate a COL24A1 variant - BMI interaction with PTB risk in AA women

Hong et al 2017 Nature Commun
Increasing Penetrance

- Highly penetrant gene variant: All (or nearly all) will develop disease.
- Moderately penetrant gene variant: Most will NOT develop disease – and many with disease will not have variant.
- Combination of weakly predictive gene variants: Weakly predictive gene variant
Other contributors to risk of PTB

- Pregnancy characteristics
  - Age (low and high); pregnancy spacing; multiple pregnancy; short cervical length
- Behaviors – e.g., smoking
- Co-morbidities – e.g., genitourinary infections
- Social disadvantage/poverty
  - Nutritional deficiencies; low education; limited access to prenatal care
- "Maternal Stress"

Monangi et al Seminars Perinatol 2015
Frey & Klebanoff Seminars Fetal & Neonatal Med 2016
Complexities of "race"

A social construct
- Definitions vary in different societies and at different historic periods
- A component of social hierarchy

Correlated with both
- Geographic ancestry
- Differential physical & social health exposures

Encompasses considerable genetic and cultural heterogeneity
“Black” - Nigeria - South Africa – Ethiopia - Madagascar
“White” - Finland - Spain –Bulgaria – Ireland
A role for epigenetics?

Changes in gene expression, related to physical changes in genomic environment, rather than DNA code - & may be transmitted over 1-2 generations

Example: DNA methylation

- Prenatal/early childhood adversity a potential cause of adverse epigenetic changes
Continuum of genetic risk

- Mostly not genetic
- Multifactorial
- Mostly genetic

- Chicken pox
- Most diseases
- Cystic fibrosis
Complexities of PTB

- “PTB” likely consists of several subtypes and varying etiological pathways
  - One study found evidence for 5 major groups of PTB (Esplin et al Am J Ob Gyn 2015)

- Defining and measuring some non-genetic contributors is difficult – e.g.:
  - Usual measures of SES do not capture all social disadvantage experienced by minorities
  - Many different factors may contribute to maternal stress
Challenges and benefits of gene-environment studies

Hypothetical scenario:
Assume preliminary evidence supports two risk factors for PTB:
- Gene Variant X
- Maternal Stress, measured by validated self-report tool

What are the implications of different potential interactions?
1. Effect of maternal stress is greater when Gene Variant X present

Measured effect of maternal stress depends on frequency of Gene Variant X

Based on Khoury et al, AJHG 1988; 42:89
2. Effect of Gene Variant X is greater when maternal stress is present

**Measured effect of Gene Variant X depends on frequency of maternal stress**

Based on Khoury et al, AJHG 1988; 42:89
3. Both maternal stress and Gene Variant X required for increased risk

Measured effect of each factor depends on presence & frequency of the other

Based on Khoury et al, AJHG 1988; 42:89
Challenges and benefits

- Failure to account for environmental and social modifiers of genetic risk could
  - Result a false estimate of genetic contribution
  - Miss environmental and social risks of greatest impact

- Over-estimate of genetic risk could lead to fatalism and group stigma

- Study of gene-environment interaction could
  - Help to explain differential response to non-genetic risk factors
  - Contribute to defining PTB subtypes
  - Identify critical biological pathways
Conclusions

- Given limited heritability of PTB and lack of major gene effects, social/environmental factors are likely to play a dominant role in PTB risk, both within and between groups.

- Genetic risk of PTB must be studied in context of other contributors to risk.

- Gene-environment analysis offers an opportunity to better define PTB subtypes and potential opportunities for intervention.