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# Racially classified social group tobacco-related health disparities: what is the role of genetics?


## ABSTRACT

Certain racially classified social groups suffer disproportionately from tobacco-caused morbidity and mortality. Recent advances in genetics are leading researchers to examine variables that may account for this. However, it is critical that investigators proceed with caution and utilize transdisciplinary approaches. A number of fundamental questions might be used to stimulate consensus building in this area of science. What is race and how should its complexity be operationalized? Is it possible/likely that pharmacogenetics will allow us to match smokers with cessation strategies based on a gene-psychological profile? What are the most important conceptual and methodological issues for a research agenda in this area?


**Keywords** Disparities, genes, race, tobacco.

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## INTRODUCTION

Particular racially classified social groups (RCSGs) (for further discussion on racially classified social group characterization see King [1]) bear a disproportionate burden of tobacco-related health disparities (TRHDs) [2]. In this current issue, Fagan *et al*. [3] define TRHDs as differences in exposure to tobacco, tobacco use initiation, current use, number of cigarettes smoked per day, quitting/treatment, relapse and the subsequent health consequences among specific population groups, as well as differences in capacity and infrastructure and access to resources. Reducing RCSG TRHDs is a national public health priority [4]. A growing body of research is documenting the importance of genes in understanding tobacco-related etiology (see reviews by [5,6]). Studies have reported that smoking initiation and maintenance, nicotine metabolism, nicotine dependence and response to smoking cessation treatment are significantly attributable to both genetic and social heritability (i.e. [7–10]). Although the completion of the sequencing of the human genome [11] might make investigation of the role of genetics in understanding differences in risk factors for TRHDs an attractive scientific approach, it is critically important to understand reasons why investigators might examine genetics as an explanation for RCSG differences in TRHDs and what is at stake [12]. The purpose of this paper is to stimulate dialogue as to why and how investigators might reasonably address this issue.

## HISTORICAL OVERVIEW OF THE 'RACE' CONSTRUCT

There has been debate over whether there is value in continuing to utilize the 'race' construct in discussing and examining health status among populations, with some arguing for the continued use of 'race' and others recommending abandonment of the construct altogether [13–17]. (The term 'race' is enclosed in quotations because of its varied use and interpretations. The author prefers to utilize the term racially classified social group (RCSG) in recognition that this population descriptive is socially constructed.) In order to understand the debate and what is at stake, researchers must consider the historical and scientific background of the term 'race', the social and political consequences of the term's use and the connection of these socio-political consequences to RCSG TRHDs in the United States.

The features that have been used to classify and distinguish individuals of a particular 'race' (i.e. skin color, eye shape, hair texture, etc.) have not been stable across US regions or constant over time [18–29]. For example, the Office of Management and Budget (OMB) racial categories have changed since their inception [21]. Furthermore, how 'race' is defined in the United States is very different from how 'race' is defined in other parts of the world (i.e. [21,22,30,31]). 'Racial' definitions have evolved across eras according to complex social contextual conditions, based primarily upon power relations within a given society [23]. In the United States, the origins of 'race' evolved out of the context of the African American slave trade in America by white European settlers as well as the desire for these settlers to covet and obtain land from Mexicans and Native Americans [25,32–34]. If these new white European settlers could demonstrate the biological inferiority of African Americans and other RCSGs over white Americans, they could then rationally legitimize their genocidal systems and

exclusionary behaviors. Biological science and medicine, driven by this social agenda, soon thereafter began efforts to document the superiority of white Americans over all other RCSGs in the United States and legitimize the use of 'race' based upon phenotypic attributes that were solely posited to be determined biologically [22,35,36].

Over the last two decades, biological science via the Human Genome Project has demonstrated that all humans share 99.9% (approximately 3 billion DNA building blocks) of their genetic make-up and the resulting 0.1% (approximately 3 million DNA building blocks) difference that does exist is not likely to have an effect on phenotype (i.e. [37]). Furthermore, it is difficult to characterize individuals reliably and discretely as being of a particular 'race' based upon phenotypic attributes [38]. For example, an individual could have brown skin and/or curly hair texture and be classified as belonging to two or more 'races'. Therefore, attempts to use genetic and phenotypic markers as a substitute for 'race' have not been widely accepted [39–43].

'Race' is largely a socially constructed concept created by institutional and ideological forces defining and maintaining 'racial' superiority. Thus, those who want to do away with racial terminology argue that 'race' as a natural biological construct delineated via discrete phenotypic attributes does not matter. However, those arguing for the continued use of racial terminology believe that 'race' as a very contextually relevant social construct does matter because of disparate social, economic and health consequences between RCGSs.

## GENETICS AND TOBACCO-RELATED HEALTH DISPARITIES AMONG RACIALLY CLASSIFIED SOCIAL GROUPS

The challenge of addressing TRHDs among particular RCSGs is important because tobacco is the leading cause of preventable disease and death in the United States, with respect to morbidity and mortality caused by cancer, heart disease, stroke, complications of pregnancy and respiratory illness. RCSG disparities clearly exist along the tobacco continuum (i.e. from experimental behaviors to tobacco-caused lung cancer) and have been documented widely (as an example see [3]). It is imperative that research scientists approach the challenge of reducing these RCSG TRHDs with innovative lines of inquiry and methodology because, since the call to eliminate these disparities—prompted by the 1998 Surgeon General report on tobacco use among US racial and ethnic groups [2]—little progress has been made in alleviating these inequalities.

Researchers are challenged to develop innovative methods to examine, understand and address RCSG TRHDs. Research on the genetics of tobacco has suggested that genetic factors play a role in the tobacco use trajectory (i.e. [5,9]). Studies have determined genetic influences on smoking initiation [7,44], smoking persistence [45,46], tobacco dependence [46–50], nicotine metabolism [10,51,52], smoking cessation [48,53–55] and smoking-related disease [56,57] and some studies are framing these findings along RCSG distinctions [i.e. 49,58–60].

One example of TRHD genetic research that has been presented along RCSG distinctions is variability in nicotine metabolism. Clearance of nicotine from the body could affect smoking behavior as well as exposure to other tobacco constituents. Studies have found that cotinine (the primary proximate metabolite of cotinine) levels are higher among African Americans than other RCSGs [61–65]. It has been proposed that the higher levels of cotinine found among African American smokers is due to the slower metabolism of cotinine to its conjugates in African Americans compared to white Americans [66,67]. Some research has explored a genetic basis for the slow nicotine/cotinine metabolism phenomenon. The cytochrome P4502A6 (CYP2A6) gene has been shown to display genetic variation with a wild-type and two null alleles [68,69]. Individuals carrying a CYP2A6 null allele exhibit decreased nicotine metabolism. However, genetic studies to date have not demonstrated significant differences in CYP2A6 alleles among African Americans compared to other RCSGs. The logic of such studies is founded on the notion that RCSGs may have distinct genetic characteristics that result in different biochemical processes such as variations in nicotine metabolism. Such studies could contribute to a trajectory of research that links 'race' and genetics to disease and ultimately the development of targeted pharmacotherapeutics for nicotine dependence based upon presumed genetic differences between RCSGs, which may or may not alleviate RCSG TRHDs or simply disguise other biopsychosocial explanations for TRHDs among RCSGs. Specifically, the nicotine metabolism distinctions, as they have been presented, outside a social context, may continue to legitimize views of genetically derived biological differences, encouraging existing racial stereotypes and promoting new ones. [Recent research by Fernander & Schumacher (submitted manuscript) found no support for an association between cotinine levels and CYP2A6 allele activity among African American female smokers, but instead found associations between life stress and both cotinine levels and carbon monoxide levels measured in expired air. This finding emphasizes the need for researchers to look beyond genetic explanations to other biological processes and psychosocial mechanisms that may explain elevated cotinine levels among African Americans.]

## THE ROLE OF PHARMACOGENOMICS AND TOBACCO PHARMACOTHERAPY

Despite observations that within-RCSG genetic variation is much greater than variation between RCSGs (i.e. [37]), there is a growing number of privately and publicly funded cell repositories collecting DNA samples by RCSG, reifying further the relationship between 'race' and genes. The promotion of such repositories, if not evaluated carefully and critically, might lead one to assume that the supposed genes that determine one's health status would also determine the 'race' of an individual (or vice versa; see the following for a full discussion on this topic [13,15,70–72]).

Given the evidence that there are smaller genetic differences across RCSGs than among RCSGs, an assumption that genetics might be a significant and/or sole contributor to RCSG health disparities does not appear warranted. Furthermore, such a view may encourage the preservation of 'racialized science and medicine' (which seeks to explain human population differences in health as the consequence of biologically based differences between 'racial' groups) and/or the 'racialization of pharmacogenomics' (where rather than examining how an individual's genetic inheritance affects the body's response to drugs, investigators examine how one's 'race' affects the body's response to drugs) [18]. For example, the recent approval by the United States Food and Drug Admininstration for the company Nitromed, Inc. to market BiDil® as the first ever 'race-specific' pharmacotherapeutic treatment for heart disease among African Americans reflects the reality that medical science continues to be wedded to the idea that 'race' is a proxy for biological variation, and positions 'race-based' medicine as a tool to eliminate disparities in health status among RCSGs (it is possible that BiDil's effects are owed to functional associations of treating heart failure due to high rates of hypertension among African Americans, rather than the fact that African Americans as a group are more responsive to BiDil's pharmacotherapeutic effects). The success in the formulation and marketing of BiDil combined with recent pharmacogenetic trials of nicotine replacement therapy [53,55,73–77] may act as precursors to tobacco researchers, clinicians and pharmaceutical companies to market tobacco cessation pharmacotherapies as biologically 'race-based' tobacco cessation pharmacotherapies (i.e. nicotine replacement therapies) rather than cessation therapies for individuals with specific etiological profiles.

The potential of genomic technology and molecular biology to decrease disease among individuals is extraordinary. The anticipated benefits of pharmacogenomics include: more powerful medicines; better, safer drugs; more accurate methods of determining appropriate drug dosages; advanced screening for disease; better vaccines; improvements in the drug discovery and approval process; and a decrease in the overall cost of health care [78]. However, caution is warranted when it comes to proposing to utilize pharmacogenomics to address RCSG TRHDs because the field of tobacco research, to date, has not demonstrated that there are significant genetic differences that explain TRHDs between RCSGs in the United States. The field of pharmacogenomics and the potential of 'personalized medicine' (specific genotypes interacting with particular environments to determine customized treatment) is indeed an innovative approach to achieve health and decrease tobacco-related disease and mortality among individuals. However, rather than focusing upon improving the health status of individuals based upon biological profiles, as the field of pharmacogenomics posits to do [10,79,80], some of the focus appears to be upon improving the health status of populations—including 'biologically defined races'. Such emphasis encourages and prolongs what is now the ancient yet lingering existence of 'race-based' science and medicine and RCSG health disparities [18,42,81–83].

## UNANSWERED QUESTIONS

Given that 'race' continues to be a critical socio-political construct that defines population groups in the United States, Lee [18] posits that in order to address research questions pertaining to RCSGs, investigators must first develop an explicit working definition of what 'race' means in the specific social context under investigation, particularly as 'race' has been determined to be a fluid social construct [39]. Jones [84] recommends that in order to understand the context in which data concerning 'race' is being collected and to gather more precise data, measures that assess ancestry, income status, neighborhood characteristics, etc. that give more concrete meaning to the reality of the psychosocial and genetic circumstances should be utilized.

Although familial studies suggest that genetic factors influence tobacco use, nicotine dependence and morbidity, these genetic studies may be confounded due to the fact that families share similar environments as well as genes. Thus, researchers should not abandon traditional methods of examining RCSG TRHDs via social forces for a solely genomic approach. Rather, because the genetic difference of 0.1% across some RCSGs may exist due to psychosocial factors, researchers must develop innovative methods for conducting research to explore biopsychosocial interactions that may explain RCSG differences in TRHDs. More importantly, interdisciplinary teams of research scientists must come together and develop general consensus regarding how to address ethical, social, legal and political issues as they relate to research

 

investigating the interaction of genes and psychosocial factors on TRHDs within and among RCSGs. Building upon the issues and recommendations posed by Shields *et al*. [12], Stevens [85] and Bonham, Warshauer-Baker & Collins [37] regarding the use of 'race' in genetic studies, the author presents an initial uncomprehensive list of questions to promote discourse and consensus building between investigators across disciplines who are committed to understanding and eliminating TRHDs among RCSGs:

1 How do researchers ascertain a legitimate understanding of the historical legacy of 'race' and remain mindful of this history as they conduct investigations in the area of RCSG TRHDs?
2 Is there a way to develop an acceptable consensus on the definition of 'race' across the multiple disciplines of biology, genetics, medicine, epidemiology and the social and behavioral sciences?
3 Is the OMB's classification system of 'race' sufficient to examine the influence of genomics on TRHDs among RCSGs? If not, how should investigators interested in studying TRHDs among RCSGs operationalize most appropriately the construct of 'race' as a research variable?
4 How do investigators determine whether there are valid reasons to assess 'race' in investigations linking genetics and TRHDs among RCSGs? (For example, what are the pros and the cons of using 'race' as a variable in genomic studies on TRHDs?)
5 Are there more salient variables other than 'race' (i.e. other biological, psychological or social factors) that are more pertinent on TRHDs among RCSGs? If so, what are they and how should they be operationalized?
6 How do investigators build and expand upon interdisciplinary interactions between geneticists and social and behavioral science researchers who examine TRHDs among RCSGs? Furthermore, how can resources be pooled to stimulate, encourage and maintain such collaborations?
7 How do investigators interested in TRHDs develop innovative models and protocols to analyze appropriately data generated from genetic–psychosocial interactions?
8 How will the field of pharmacogenetics improve smoking cessation rates on an individual level? Do such advancements have positive or negative implications for reducing TRHDs among RCSGs?
9 How will the field ultimately be better able to match smokers to cessation pharmacotherapies based upon their gene–psychosocial profile? Does this matching have implications for RCSGs? If so, how can the creation of a pharmaceutical apartheid be avoided?
10 How do investigators oversee/protect the ethical, legal and social implications of genomic research as it relates to the bioethical principle of justice in TRHDs among RCSGs?
11 What types of specific future research agendas are critical to advance knowledge in the area of TRHDs and genetics among RCSGs?
12 How do investigators in this field disseminate findings to reduce, if not eliminate misinterpretations, misrepresentations, or oversimplifications of the role of genetic factors on TRHDs among RCSGs?
13 What are the implications of results of investigations in the area of TRHDs and genetics among RCSGs on public health policy and programs?

## SUMMARY

TRHDs among RCSGs in the United States make it clear that the socio-political construct of 'race' matters. The introductory discourse presented is not intended to provide answers to the inexhaustive list of questions posed; rather, the goal is to initiate intellectual, scientific, practical and ethical dialogue among nicotine and tobacco researchers as we seek to develop interdisciplinary framework(s) to eliminate TRHDs among RCSGs. Although the goals of the HapMap Project (formerly the Human Genome Project) are to provide tools to enhance our understanding of the genetic contributions to disease [86], the field of pharmacogenomics alone will not provide a cure for TRHDs among RCSGs. Although the field of genomics may provide limited direct knowledge regarding TRHDs among RCSGs, the field of genomics may be a powerful tool to understand the influence of genetics on the etiology/epidemiology of tobacco-related disease among RCSGs when placed within an appropriate psychosocial context. Furthermore, much about the way in which psychosocial pathways give rise to TRHDs among RCSGs is unexplained. *Ceterus paribus*, how genes and psychosocial factors might interact in the formation of TRHDs among RCSGs is largely unchartered territory. It is imperative that the interaction of psychosocial factors with genetics is explored appropriately by an interdisciplinary team of investigators to address the challenge of tobacco-related disparities early in this century (see Fernander, Shavers & Hammons [87] and Moolchan *et al*. [88] in this issue, for further elaboration on multi-disciplinary and multi-factorial approaches to examine TRHDs). It is critical that the field of nicotine and tobacco research continues in its commitment to decreasing TRHDs among vulnerable RCSGs using as much scientific knowledge and methodological tools as possible, while at the same time not contributing to traditional 'race-based' approaches to science that have led previously to the racialization of medicine.

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