Genome-Wide Association Studies in Africans and African Americans: Expanding the Framework of the Genomics of Human Traits and Disease

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Abstract
Genomic research is one of the tools for elucidating the pathogenesis of diseases of global health relevance and paving the research dimension to clinical and public health translation. Recent advances in genomic research and technologies have increased our understanding of human diseases, genes associated with these disorders, and the relevant mechanisms. Genome-wide association studies (GWAS) have proliferated since the first studies were published several years ago and have become an important tool in helping researchers comprehend human variation and the role genetic variants play in disease. However, the need to expand the diversity of populations in GWAS has become increasingly apparent as new knowledge is gained about genetic variation. Inclusion of diverse populations in genomic studies is critical to a more complete understanding of human variation and elucidation of the underpinnings of complex diseases. In this review, we summarize the available data on GWAS in recent African ancestry populations within the western hemisphere (i.e. African Americans and peoples of the Caribbean) and continental African populations. Furthermore, we highlight ways in which genomic studies in populations of recent African ancestry have led to advances in the areas of malaria, HIV, prostate cancer, and other diseases. Finally, we discuss the advantages of conducting GWAS in recent African ancestry populations in the context of addressing existing and emerging global health conditions.

Introduction
Since the first genome-wide association studies (GWAS) publication a few years ago, there has been a significant increase in studies that use GWAS as a tool to identify genetic variants associated with communicable and non-communicable diseases. GWAS have also been used to identify variants that influence human traits including eye color, hair color and anthropometric characteristics [1–3]. Genomic variations have been associated with drug resistance and treatment outcome [4]. The number of GWAS and pharmacogenomics studies that have identified single nucleotide changes associated with
An Overview of Diversity in GWAS Data

Despite the expansion of GWAS tools to identify disease- or trait-related variants in human populations, adequate studies inclusive of diverse populations are lacking. Previous assessments of the representation of non-European populations in GWAS utilizing publically available databases have revealed significant underrepresentation of these populations in published GWAS [12–14]. We queried the Research Portfolio Online Reporting Tools (http://projectreporter.nih.gov/reporter.cfm) to determine the numbers of NIH-funded GWAS focused on or utilizing non-European populations. Our search yielded 2,267 current NIH-funded studies matching the search term ‘genome-wide association studies’ as of mid 2014. For a more accurate comparison, we used search terms such as African American, Hispanic, or Jewish ancestry also utilized by aforementioned publications. For ongoing studies (e.g. 2011) in the National Institutes of Health Research Portfolio Online Reporting Tools, GWAS accounted for only ~14, ~3, and ~<1% for African American, Hispanic, or Jewish ancestry populations, respectively. Subsequent analysis of published GWAS from PubMed using the same search terms produced 4,942 publications, of which African Americans accounted for ~3% with Hispanics and Jewish accounting for <1%, which are essentially in agreement with the previous reports. From the 2011 data, African Americans represented the largest non-European population included in GWAS.

Recently, several GWAS have included African ancestry populations in their discovery (initial stage) or replication datasets. From January 2009 to May 2010, 21 such studies have been included in the National Human Genome Research Institute (NHGRI) GWAS catalogue [13]. We chose to use the NHGRI GWAS catalogue for our review on African Americans and African ancestry populations because the catalogue includes literature that meets stringent inclusion criteria (http://www.genome.gov/gwastudies/). Moreover, analysis using the NHGRI GWAS catalogue produced results that reflect paucity of data for the African American population. In this review, we examine and briefly summarize several GWAS in diasporic African populations and continental African populations from publications in the NHGRI GWAS catalogue until mid 2014.

Advantages of Conducting GWAS in African Americans and African Ancestry Populations

Arguments have been made for broader inclusion of populations of African ancestry in GWAS [12–16]. With the underrepresentation of African ancestry populations in GWAS, one might ask: what is the utility in genetically characterizing populations of African ancestry? The occurrence of some genetic variants shows considerable frequency variation across populations which also includes the frequency of the risk allele, frequency of causal and correlated variants, and prevalence of diseases. Genetic determinants of disease and their effect sizes have also been shown to vary significantly between European and non-European populations such as populations of African ancestry [12]. It has been demonstrated that variants associated with diseases found in European ancestry populations do not always replicate in non-European populations [9, 17, 18]. GWAS conducted in European populations have frequently failed replication in non-European populations for several reasons, including differences in allelic architecture, linkage disequilibrium, and confounding of environmental factors across populations [14]. As the continent where the human species originated, Africa harbors populations with longer histories compared to European populations [19, 20]. GWAS provide opportunities for characterization of longer population histories and greater genetic heterogeneity found in African populations, allowing more accurate construction of ancestral haplotypes which cannot occur in non-African populations [21]. If one cannot determine the original haplotype, African populations offer opportunities to determine the evolutionary histories of these variants [22]. For example, the genetic origins of fragile X syndrome via haplotype analysis of the X chromosome have been well characterized in European populations [23]. However, the haplotypic origins of this mutation in African populations are yet unknown, even though fragile X syndrome has been found in an African population [24]. This syndrome and other Mendelian disorders offer a model to understand the evolutionary history of monogenic dis-
orders as humans migrated out of Africa. The information could also contribute to greater understanding of recombination and evolution of genes in the X chromosome. Thus, inclusion of populations of African ancestry and other diverse populations in GWAS is critical to understanding human variation in both monogenetic and more complex disorders.

Notable Discoveries from GWAS in African American and African Ancestry Populations

Non-Communicable Diseases

GWAS have had considerable influence on the identification of genetic variants associated with non-communicable diseases. We have identified several GWAS on non-communicable diseases and also traits that have been conducted with African ancestry populations. Publications from these studies are listed in online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000367962). Asthma is a complex non-communicable disease that significantly affects both the young and old. Approximately 15 million Americans are affected, with ~5,500 deaths attributed to complications [25]. Hospitalizations for asthma are 2–3 times higher for African Americans compared to other ethnic groups [25, 26]. GWAS exploring the genetic basis of this multifactorial disease in African ancestry populations have identified several associated genes (online suppl. table 1). Susceptibility loci for asthma were first identified in children of European ancestry (from Europe and the US) and then replicated in African American children [27]. Variants in the genes CRBI and PDE4D were associated with asthma in children of European ancestry [27, 28]. For African American populations, association with asthma was found for variation in the gene DENND1B, but not in CRBI or PDE4D [27, 28]. SNP variants found in intergenic regions near ADRA1B, PRNP, GNA13, and DPP10 have been implicated in asthma and allergic diseases in African American and African Caribbean populations, but have not been replicated in European populations [29]. PDE4D, a regulator of airway smooth muscle contractility has been replicated in several European and Hispanic populations, but not in populations of recent African origin [28]. Over 43 genes associated with asthma have been identified [30]. However, few of them have been replicated via subsequent GWAS in other populations [30].

Asthma is a serious chronic disorder characterized by airway inflammation [31]. The inflammatory process in asthma is characterized by a significant elevation of white blood cell count (e.g. eosinophils, neutrophils and other white blood cells) [32]. GWAS have provided evidence that variation in white blood cell count in African Americans has a genetic component. GWAS have replicated genes on 17q21.1 in 2 cohorts of African Americans [33, 34]. Interestingly, 17q21.1 is also associated with inflammation and with childhood asthma [35]. This provides evidence suggesting that in some disorders the genetics of traits and diseases could be similar, as observed in white blood cell count, asthma and 17q21.1 [33].

Unlike asthma, the primary genetic variant underlying sickle cell disease (SCD) has been identified, but the tools of GWAS are being used to determine the nature of the genetic modifiers associated with phenotypic diversity in SCD. Genes implicated in SCD severity include BCL11A, which has been shown to modulate fetal hemoglobin levels and has been confirmed in GWAS in African Americans [36]. Sex-stratified analysis indicated GLP2R is an important modifier of fetal hemoglobin in males [36]. There has not been an established connection between SCD and asthma. Evidence supports asthma and SCD as distinct comorbid conditions [37]. However, some argue that the high prevalence of asthma in individuals with SCD suggests that the underlying mechanisms of the 2 diseases might be similar [38, 39]. GWAS of sickle cell anemia in African Americans have produced associations with OTUB3 and KCNK6 [40]. KCNK6, a member of the K+ channel protein family, is expressed in cardiomyocytes and in airway epithelial cells [41, 42]. KCNK6 also showed differential expression in pulmonary artery endothelial cells when exposed to sickle cell plasma [40]. This suggests an uncharacterized role of KCNK6 in SCD. For both asthma and SCD, the complexity of the phenotype would suggest that genetic heterogeneity is a major contributor to both diseases, so careful classifications of individuals based on clinical subphenotype or other classification schemes and the use of appropriate genetically matched controls might be worthwhile.

GWAS have identified several loci that are associated with prostate cancer (online suppl. table 2). Eeles et al. [43] found 9 SNPs in 7 genomic regions dispersed among 5 chromosomes in patients with prostate cancer. Some of these variants were replicated in GWAS of African American males. However, the majority of associations were not replicated, which may have been due to the small sample sizes of the 2 studies [44]. Several of these genes including TET2, NXX3.1 and ITGA6 have been found to have oncogenic properties. ITGA6 is necessary for tumor formation in breast cancer cells, but its expression is down-

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regulated in cervical cancer [45, 46]. Some groups have reported TET2 associated with hematological cancers including myeloid leukemia and thrombocytosis [47–49]. NKX3.1 encodes an androgen-regulated transcription factor expressed in luminal epithelial cells in the prostate [50]. The function of NKX3.1 is to prevent other genetic insults from initiating tumor growth because overexpression of NKX3.1 in vitro inhibits cell proliferation and formation of anchorage-independent cell groups, which has been associated with early stages of prostate tumorigenesis [50]. Additional evidence suggests that the loss of NKX3.1 leads to aberrant regulation of gene clusters, which is a major initiating factor for prostate tumorigenesis [50]. NKX3.1 has an indispensable role in prostate cancer and is regarded as the ‘gatekeeper’ to prevent tumorigenesis [50, 52]. Subsequent GWAS using Tobagonian men as the replication sample have not found an association between prostate tumor development and TGF-BR3, a tumor suppressor with a significant role in prostate tumor development [53, 54]. These data suggest that the mechanism which produces tumorigenesis in prostate cells or other cell types could have different associated genetic variants in some non-European populations.

Recently, a GWAS and a family-based association study were conducted on podoconiosis (geochemical non-filarial elephantiasis of the lower legs). So far, this study is the only published GWAS on non-communica
des among continental African population groups. The findings have shown that variants in HLA-DRBI, HLA-DQBI and HLA-DQA1 genes are associated with risk of susceptibility to podoconiosis [55]. Further evidence for the HLA class II association was found with HLA typing that showed HLA-DRBI*0701, HLA-DQA1*0201 and HLA-DQBI*0202 are risk variants. These alleles may have a functional role in presenting antigens (currently unknown) to T cells and imply that podoconiosis may be a T-cell-mediated inflammatory disease [55].

In the past decades, considerable progress towards understanding the neurogenetics of social behavior has used twin studies to establish the heritability of several behavioral phenotypes [56]. These studies have produced substantial amounts of data including the association of oxytocin and vasopressin with several aspects of social behavior and also suggest that structural variants might predispose families or individuals to such behaviors and neuropsychiatric disorders [56–58]. Many of these studies need replication in non-European populations.

Numerous reports have explored the genetic underpinnings of schizophrenia (online suppl. table 1). This psychiatric disorder is a complex disease with heredity often playing a substantial role in predisposition to the disorder [59]. Several genes have been implicated in schizophrenia; however, previous findings have not been replicated, causing some to argue that new approaches and fundamental rethinking of schizophrenia are required [60, 61]. For example, HIST1H2AG, HIST1H2AB and other genes are implicated in schizophrenia in African Americans and populations of European ancestry without achieving genome-wide significance [62]. Bipolar disorder is a neuropsychiatric disorder characterized by episodic mania and depression. Similar to schizophrenia, bipolar disorder has a significant genetic component with heritability of ~80% [63]. GWAS of this disorder in African Americans and European ancestry populations yielded an association with DPY19L3 which was found to be not significant after correcting for genome-wide multiple testing [64].

Several groups have used GWAS to understand the genetic components of dependent behaviors ranging from alcohol dependence to smoking behavior [65]. In European ancestry populations, a variant located in a potential transcription factor-binding site upstream of IL15 is correlated to smoking frequency [65]. Cigarette smoke has been found to have decreased IL15 expression and diminished activation of downstream signaling molecules [66]. It would be interesting to look at the mRNA/protein levels of these individuals to determine the expression of IL15. This would suggest a mechanism of smoking behavior that could also be associated with interleukins characterized in immunity [67]. If IL15 is truly associated with smoking behavior, therapeutic interventions could be developed based on the characterized function of IL15 in immunity [68]. For other behaviors, including alcohol dependency, GWAS in which African American patients were included have not yielded SNPs with genome-wide significance [69, 70]. These studies have found areas in the genome that are correlated with dependence behaviors. For example, a region on chromosome 11 is described as a candidate locus for alcohol dependence [69]. For dependency behaviors, replication of previous associations found in African Americans has been difficult.

GWAS exploring cardiovascular diseases have revealed several association signals (online suppl. table 1). GWAS of African American hypertensive patients found associations with genes involved in systolic blood pressure including an Na/K+Ca exchanger (SLC24A4), and a class of calcium channel blockers (CACNA1H), PMS1, YWHAZ, and IPO7 [71]. With the largest sample size using multiple cohorts of American Americans, Fox et al.
were not able to replicate initial genetic associations for systolic or diastolic blood pressure. They suggest that within this large multiple cohort study, several issues (e.g. the heterogeneity in blood pressure measurement across centers, the number of individuals on blood pressure-lowering medication, antihypertensive medication, and the median age of cohorts) may have biased the results toward the null hypothesis [72].

GWAS on cardiac left ventricular hypertrophy and stroke have showed associations with variants in RAII4 and CD36 for left ventricular hypertrophy and NINJ2 and CD36 for stroke, showing that CD36 is implicated in both conditions [73, 74]. CD36 is a receptor with diverse functions including negative regulation of angiogenesis, internalizing pathogens in immune response, and facilitating lipid transport and muscle lipid utilization [75]. The lipid utilization function of CD36 is also implicated in signaling for systolic blood pressure for hypertension and adipose energy storage in obesity and diabetes [71, 75]. CD36-mediated signaling could provide an example of common signaling paradigms in which other effectors could interact between pathways of hypertension, diabetes, stroke, and cardiovascular disease. Further characterization in non-European populations of CD36 function in these different conditions is warranted.

In addition to identifying genes associated with non-communicable disorders, GWAS can also be used to identify genotypes associated with various treatment outcomes. In hypertension, variants in LYZ, YEATS4, and fibroblast growth factor receptor substrate 2 (FRS2) are associated with differential responses to antihypertensive drugs (e.g. thiazide diuretics) commonly used to regulate blood pressure [17]. In African Americans, the variant located in YEATS4 was significantly associated with good response to thiazide diuretics [17]. Thiazide diuretics can be used to distinguish good responders (patients that show improvement on diuretics) from non-responders or bad responders (patients with a negative response to diuretic medications for the treatment of hypertension).

Communicable Diseases

One of the major infectious diseases affecting sub-Saharan African populations is malaria. Studies have been conducted to characterize the regions of the Plasmodium falciparum genome under positive selection in order to monitor the development of drug resistance in the parasite [18]. Additionally, GWAS have utilized cases in endemic areas to determine loci in the human host that influence disease outcomes [76]. The rationale is that host genetics accounts for ∼25% of the risk for life-threatening malaria, or more specifically, the anticipated effects of hemoglobinopathies (e.g. α-thalassemia) would only explain ∼2.5% of the total variation. Thus, it is hypothesized that protective genes of hemoglobinopathies result in small population effects suggesting that malaria resistance is under multigenic control with each individual gene having a relatively small impact [77]. Jallow et al. [76] identified genetic variants close to SOCI, HBB and DDC as protective against severe malaria in children (online suppl. table 3). SOCI is a scaffolding protein with multiple functional motifs mediating interactions with other signaling molecules [78]. Similar to other Gab proteins, SOCI is involved in signaling pathways mediated by receptor and non-receptor protein tyrosine kinases and is important in immunity [79]. Dihydroxyphenylalanine decarboxylase converts specific chemical precursors to dopamine and serotonin via decarboxylation which also functions in cellular immunity and resistance to parasitic infections via melanization [80]. The hemoglobin β locus (HBB) has been replicated in several studies as a major locus for malaria resistance and is reviewed in other papers [81, 82]. The locus has been under positive selection in humans because of its role in malaria resistance [83]. These data suggest that resistance to malaria infection also includes immune response mechanisms, which need further characterization.

GWAS have also been performed to identify genetic variants associated with pulmonary tuberculosis in West Africans [84]. The nearest genes to the variants identified were GATA6, CTAGE1, RBBP8, and CABLES1 along with several unannotated open reading frames [84]. GATA6 is a transcription factor identified as regulating the local epithelial innate immune response, with an essential function maintaining the lung epithelium [85, 86]. In addition, other reports indicated that GATA6 regulates the temporal appearance and number of bronchialveolar stem cells, making GATA6 essential for proper lung epithelial regeneration [87]. Human GATA6 expression has a protective function in lung epithelial cells exposed to Pseudomonas aeruginosa [85]. Other genes involved in immunity have also been identified in diseases caused by viruses. For example, HLA-B located at chromosome 6p21 has been found to influence the HIV viral load in both African Americans and Europeans [88–90]. Pelak et al. [89] found that HLA-B*5703 influences the viral load variation in African Americans. HLA-B*5703 has not been found in European populations studied and has an allele frequency of ∼5.8% in the Yoruba, indicating that its presence in African Americans is likely due to African ancestry [91]. The closely related allele HLA-B*5701 is...
also important in HIV-1 control; it has an allele frequency ~6.1% in Europeans, but has not been found in the Yoruba [91, 89]. Other determinants of HIV infection and viral load could lie within the HLA locus which has also been linked to HIV viral load [88]. In general, these data suggest that the mechanistic control of HIV in different populations (i.e. African Americans and Europeans) is similar [90].

One major influence on treatment outcomes for hepatitis C viral infections is a variant upstream of IFNL3, encoding interferon-λ-3 [6]. This variant is associated with sustained absence of detectable virus or a sustained virological response (SVR). Using GWAS, Ge et al. [6] observed that almost half of the difference in SVR between populations could be accounted for by the difference in the frequency of the C allele between African Americans and Europeans. In viral infections, the mechanism of clearance seems to suggest that the variants are similar across populations, but it is the frequency of the variants that lead to differences in responses in diverse populations [6]. Additional research is needed to determine common variants that influence viral response.

Lessons from Previous GWAS

Some lessons have emerged from GWAS that can inform other genomics-related studies. The unique lessons acquired from studies of non-European populations, such as African Americans, Caribbeans, Hispanic Americans, and Africans are largely due to their increased genetic diversity. First, GWAS in one African population or diasporic African population may not always be replicable in another African or diasporic African population because of population diversity and allele frequency differences. Thorough understanding of population structure between and within these populations is needed when performing GWAS analysis. Currently, reference sequences for the majority of African or diverse populations are not available (with the exception of the limited number of African populations in the HapMap and 1000 Genome Project databases). To circumvent this major problem, DNA sequencing is required to characterize population genetic diversity which can be used to generate very robust results [76]. This method overcomes issues of incorrect imputation due to the lack of inappropriate reference populations. Second, the use of genetically matched controls from reference populations is also critical in GWAS. The introduction of non-genetically matched controls can decrease the statistical power to detect associations in GWAS or may result in spurious association because of population structure. Third, careful ascertainment of the phenotype is crucial to prevent residual confounding effects of unmeasured phenotypes [9]. Fourth, generally weaker linkage disequilibrium pattern in African populations is both an advantage and a disadvantage. Weaker linkage disequilibrium allows for improved localization of associations. On the other hand, coverage is lower, and tag SNPs are less efficient in African or African ancestry populations, making the initial discovery of association signals using the same commercial platforms used in European population GWAS less efficient in these populations. Moreover, improved localization and refinement of association signals have been demonstrated in African Americans and African populations leading to successful discoveries in infectious disease susceptibility [76, 92]. Some initial studies using European populations have failed to replicate findings in African ancestry populations suggesting some phenotypes may show genetic heterogeneity between populations [14]. Finally, many GWAS that involved African ancestry populations do not have adequate sample sizes. It is recommended that investigators should use appropriate sample sizes when performing GWAS in non-European populations; essentially, the samples sizes should be larger when compared to European populations to account for additional genetic diversity within the African ancestry populations.

Limitations of current GWAS are related to both the tools and methods. Currently, many GWAS in African populations are performed using arrays designed for European populations, directly or indirectly capturing ~60% of the genomic variation in any African population, leaving 40% of these variants unassayed [93, 94]. These limitations also result in the lack of discovery of variants that could significantly contribute to the phenotype. Several non-profit entities have developed partnerships with for-profit corporations to enhance variant coverage and power of genotyping arrays for African ancestry populations. Contemporary efforts to develop an African Diaspora Power SNP Chip that aims to contribute to a deeper understanding of genetic variation particularly in admixed African ancestry populations in the Americas is underway. As part of this effort, whole genome sequencing of ~700 African ancestry samples via the Consortium on Asthma among African-ancestry Populations in the Americas has identified about 22 million novel variants, and the design of the array that includes common tag SNPs is anticipated to be valuable, particularly for admixed African ancestry populations in the Americas.
Several methods have been designed to address unique issues in assessing population stratification of populations with admixed ancestries [97–99]. These new methods improve the ability to correctly account for several confounding factors which, if not properly addressed, could lead to serious errors in modeling data.

The art of conducting genomic studies in populations identified by ancestry is as important and daunting as the science itself. The unique and shared historical, social, cultural, and economic contexts within and between populations must be taken into account throughout the conceptualization and implementation of these studies. A growing body of research is exposing and exploring the range of ethical and policy issues pertaining to informed consent, data and sample sharing, management of results and secondary findings, and other aspects of genomic research in African and African ancestry populations [96, 100–107]. In addition, ongoing community and public engagement in these and other populations involved in or affected by genomic research is increasingly highlighted as a means of building relations, facilitating understanding through exchange of information, and enhancing collaboration between researchers and communities [108–112]. As cutting edge genomic research gradually proliferates throughout Africa and the African diaspora, opportunities and challenges related to the identification and resolution of emerging issues will multiply. It is essential that our current training efforts adequately foster the development of researchers in these locations who can rigorously examine these issues.

Conclusions

GWAS have uncovered genetic variants associated with susceptibility for several different traits and disease conditions including asthma, cancer, obesity, hypertension, blood pressure, and malaria in recent African ancestry populations. GWAS involving non-Europeans such as African American and African ancestry populations have greatly lagged behind the increasing number of GWAS that have been published. Some existing GWAS that use non-European populations at replication omit these populations in the initial discovery phase, resulting in subsequent failure to replicate the associated variant(s). Failure to replicate genetic variants associated with the phenotype of interest in these populations could be erroneously attributed to differences in population structure, allele frequencies and environmental factors suggesting the need to include larger cohorts of non-European populations in both discovery and replication.
Whereas non-communicable diseases impose huge burdens on US populations, infectious diseases have traditionally been more relevant and problematic on the African continent. However, within Africa, the increase in a more sedentary lifestyle, in conjunction with high-caloric diet is contributing to increases in the prevalence of several categories of non-communicable diseases. Both the relevance of infectious diseases and increasing prevalence of disease due to lifestyle offer unparalleled advantages of African populations in understanding the genetic and environmental underpinnings of diseases in human populations. Another unique advantage of African populations in discerning the evolutionary history of disease variants and haplotypes has not been well exploited and may provide directions in understanding pathways and mechanisms of human diseases [12–14]. Finally, the potential role of genomics research with more diverse non-European populations in understanding human health disparities should be emphasized. Several projects are underway to characterize human genetic and phenotypic variation (http://1000genomes.org and http://news.sciencemag.org/scienceinsider/2010/06/uk-to-sequence-10000-genomes.html). However, without the inclusion of multiple populations of African ancestry, the data generated by these multinational collaborative efforts might have a limited benefit to humanity as a whole. Advances in genomics should help ameliorate rather than contribute to health disparities among diverse populations. With the collaborative efforts of global scientists and local communities, and the development of new data analysis capacity, state-of-the-art genomics research is poised to take advantage of humanity’s most diverse populations and return the greatest benefit in the improvement of human health.

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