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From Mummies to Modern Man:

Genomic Research to Advance Human Heredity and Health

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From Ötzi, the Tyrolean Iceman, to the royal mummies of pharaohs Akhenaten and Tutankhamun, genetic and genomic analyses of ancient deoxyribonucleic acid have shed light on the social and environmental influences on life and longevity, population dynamics, migratory patterns, dietary habits, putative and actual causes of death, and the susceptibility to congenital and acquired diseases during life more than 5,000 years ago [1–3]. For example, detailed analysis of the Ötzi genome demonstrated the presence of several single nucleotide polymorphisms associated with increased risk for coronary heart disease, ischemic stroke, sudden cardiac death, and general atherosclerosis [4]. The full impact and clinical manifestations of these genetic variants were likely not experienced because of the short life expectancy at that time. Several articles in this issue of *Global Heart* on mummies provide intriguing details on the value of genomic analyses and correlates in atherosclerosis and other diseases in ancient humans. [5–10]

For modern man, genomic analyses can also provide a unique opportunity to further explore gene-gene and gene-environment interactions that have the potential to greatly inform the prevention, detection, diagnostic valuation, treatment, and control of heritable diseases and traits. In particular, the current ability to link genetic variation to disease susceptibility, at least in rare variants and Mendelian disorders, provides an opportunity for genetic counseling and appropriate behavioral and lifestyle interventions to reduce the risk of specific diseases. However, more is known today about the genomes of Akhenaten, Tutankhamun, and their pharaonic lineage that lived more than 3,500 years ago than those of present-day Egyptians. Additionally, biomedical research in genetics and genomics involving African scientists has been limited [11]. Considering that modern human populations originated in Africa, and that genetic diversity is most profound on that continent, much can be gained by investments in this arena. This perspective presents investments made by the U.S National Institutes of Health (NIH) and the U.K.-based Wellcome Trust to advance the field of human heredity and health in Africa.

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The H3Africa Project

Recognizing the limited investment and engagement of Africa and African biomedical research scientists in human genetics and genomics, the NIH and the Wellcome Trust, in partnership with the African Society of Human Genetics established the H3Africa (Human Heredity and Health in Africa) Consortium with the goal of identifying the major scientific, ethical, and practical issues in the development of a large-scale genomics research program in Africa. As noted in the H3Africa Working Group white paper, “the model proposed for H3Africa seeks to position Africa not only as a vital resource for genetic and genomic data collection but also as the recognized scientific hub for the initiation and full implementation of modern genetic and genomics research in African populations” [11].

Specific recommendations were made for infrastructure development to include fully functional biorepositories; regional centers of excellence that will house modern genotyping/sequencing and phenotyping laboratories; clinical centers that will collect demographic, epidemiologic, and clinical data on all H3Africa participants; and a continent-wide bioinformatics network that will provide the necessary foundation for the large-scale genomic datasets [11]. Other recommendations included emphasis on education and training of African scientists in multiple disciplines, including genomics (high-throughput technologies); genetics; epidemiology; bioinformatics; statistical genetics; and ethical, legal, and social issues.

Recognizing the huge burden of infectious diseases in Africa, the initial focus of H3Africa included emphasis on tuberculosis, human African trypanosomiasis, and cancer due to infectious agents. Noncommunicable diseases of interest included sickle cell disease, rheumatic heart disease, hypertension, stroke, type 2 diabetes mellitus, and cancer. In addition, pharmacogenomics and the development of new and innovative approaches for the prevention, diagnosis, evaluation, and treatment of these diseases were highlighted. A key principle was that the choice and focus of research topic and the specific methodological approaches should reflect the interests and expertise of the African investigators who are to be the project leaders.

As stated in the white paper, the vision of the H3Africa Consortium “is to create and support a pan-continental network of laboratories that will be equipped to apply leading-edge research to the study of the complex interplay between environmental and genetic factors which determines disease susceptibility and drug responses in African populations” [11]. Today, there are 21 collaborating investigator teams funded at approximately US\$76 million; 18 of them are funded by the NIH and the remaining 3 are funded by the Wellcome Trust. As shown in Table 1, the work of the collaborating teams include developing an Africa-based bioinformatics network for H3Africa; several biorepositories; an ethical, legal, and social issues project; and tackling research themes that span the spectrum from pharmacogenomics in multiple drug-resistant tuberculosis to the genomics of schizophrenia. The Wellcome Truste funded projects include 3 collaborative networks addressing the following: 1) the genetics of rheumatic heart disease (RHDGen); 2) an integrated approach to the identification of genetic determinants of susceptibility to trypanosomiasis (TrypanoGEN); and 3) an investigation of the etiology of type 2 diabetes in sub-Saharan

Africa. The H3Africa Consortium members also collaborate on several working groups that deliberate, plan, and help harmonize H3Africa research activities. The most recently constituted working group addresses cardiovascular diseases.

H3Africa Cardiovascular Diseases Workshop

On May 30, 2014, in conjunction with the fourth annual meeting of the H3Africa Consortium (<http://www.h3africa.org/component/content/article/8-events/156-fourth-h3africa-consortium-meeting>), the Cardiovascular Working Group held an inaugural workshop in Cape Town, South Africa. The primary workshop objectives were to enhance understanding of the genetic underpinnings of the common major cardiovascular diseases in Africa and strengthen collaborations among the H3Africa investigative teams and other researchers using novel genomic and epidemiological tools to contribute to reducing the burden of cardiovascular disease on the continent [12]. Other important goals of the workshop included strengthening synergistic collaboration among H3Africa teams who are currently exploring cardiovascular diseases and their risk factors using novel genomic and epidemiological tools and facilitating an appreciation of the pathophysiological interrelationships between car-diomatabolic diseases and certain infectious diseases common in Africa [12]. This is an exciting development for global health in general and for cardiovascular health in Africa in particular. As was poignantly summarized in a recent commentary, the H3Africa consortium “ignites hope, as it will enhance the capacity of African researchers for cutting-edge research” and it may represent “the long-awaited tipping point for a revolution in bioinformatics, genomics and health research in Africa” [13].

Although each of the above developments represents good news in genomics and biomedical research, the H3Africa Consortium members recognize that, by themselves, their efforts in this endeavor will not be enough [14]. The time has now come for the global health community to leverage and build on the foundational investments made by the NIH and the Wellcome Trust in order to address compelling scientific questions about human heredity and health that a large-scale, genomics-focused, population-based research program in Africa is most suited to tackle. For global cardiovascular health research, this also represents an exciting opportunity!

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Table 1
H3Africa Consortium's collaborating centers and research projects funded by the
National Institutes of Health and the Wellcome Trust

Theme	Funding Source	Research Focus	Principal Investigator	Affiliation
Biorepository	NIH	Development of H3Africa biorepositories to facilitate studies on biodiversity, disease, and pharmacogenomics of African populations	Akin Abayomi	Stellenbosch University, Stellenbosch, South Africa
Biorepository	NIH	H3 African Biorepository (I-HAB) Initiative	Alash'le G Abimiku	Institute of Human Virology, Nigeria, Abuja
Biorepository (pilot project)	NIH	Establishment of an H3Africa Biorepository at Clinical Laboratory Services (pilot project)	Ute Jentsch	University of the Witwatersrand, Johannesburg, South Africa
Integrated biorepository (pilot project)	NIH	Integrated Biorepository of H3Africa Uganda (pilot project)	Moses Joloba	Makerere University College of Health Sciences, Kampala, Uganda
Bioinformatics	NIH	H3ABioNet: A Sustainable African Bioinformatics	Nicola Mulder	University of Cape Town, South Africa
Cardiometabolic disease	NIH	Genomic and environmental risk factors for cardiometabolic disease in Africans	Michele Ramsay	University of the Witwatersrand and NHLS, Johannesburg
Kidney disease	NIH	H3Africa Kidney Disease Research Network	Dwomoa Adu Akinlolu Ojo	University of Ghana Medical School, Accra; University of Michigan, Ann Arbor
Schizophrenia	NIH	The Genomics of Schizophrenia in the South African Xhosa People	Dan Stein; Ezra Susser Mary-Claire King	University of Cape Town, South Africa; Columbia University, New York; University of Washington, Seattle
Cervical cancer	NIH	African Collaborative Center for Microbiome and Genomics Research	Clement Adebamowo	University College Hospital, Ibadan, Nigeria
Stroke	NIH	Stroke Investigative Research and Educational Network	Mayowa Owolabi	University of Ibadan, Nigeria
Pharmacokinetics	NIH	Contribution of genetic variation to pharmacokinetic variability and toxicity in patients undergoing multidrug tuberculosis treatment in Sub-Saharan Africa	Dissou Affolabi	National Hospital for Tuberculosis and Pulmonary Diseases, Cotonou, Benin
HIV and HIV-TB infections in Sub-Saharan African children	NIH	The Collaborative African Genomics Network (CAfGEN) will probe host factors in the progression of HIV and HIV-TB infection in Sub-Saharan African children	Gabriel Anabwani, Kekitiinwa Rukyalekere, Moses Joloba, Oathokwa Nkomazana, Sununguko W. Mpoloka, Graeme Mardon	Botswana e Baylor Children's Clinical Centre of Excellence, Botswana; Baylor College of Medicine Children's Foundation, Uganda; Baylor College of Medicine, USA; Makerere University, Uganda, and University of Botswana, Botswana

Theme	Funding Source	Research Focus	Principal Investigator	Affiliation
Tuberculosis	NIH	Systems Biology for Molecular Analysis of Tuberculosis	Gobena Ameni	Addis Ababa University, Ethiopia
Febrile illnesses	NIH	Host and Microbial Genetic Determinants of Febrile Illness in West Africa	Christian Happi	Redeemer's University, Redemption City, Nigeria
Hereditary neurological disorders	NIH	Clinical and Genetic Studies of Hereditary Neurological Disorders in Mali	Guida Landouré	University Hospital Center du Point G, Bamako, Mali
Infectious respiratory diseases	NIH	The Nasopharyngeal Microbiome and Respiratory Disease in African Children	Mark Nicol Heather Zar	University of Cape Town, South Africa
Ethical, legal, and social implications	NIH	Exploring Perspectives on Genomics and Sickle Cell Public Health Intervention	Ambroise Wonkam	University of Cape Town, South Africa
Trypanosomiasis	NIH	Reprogramming of the <i>Trypanosoma brucei</i> epigenome during human infection: opportunities for new therapies	Hugh Patterton	University of the Free State, Bloemfontein, South Africa
Trypanosomiasis	WT	TrypanoGEN: an integrated approach to the identification of genetic determinants of susceptibility to trypanosomiasis	Enock Matovu,	Makerere University, Kampala, Uganda
Type 2 diabetes	WT	Burden, spectrum, and etiology of type 2 diabetes in Sub-Saharan Africa	Ayesha A. Motala	School of Clinical Medicine, Nelson R Mandela (NRMSM) Campus, University of KwaZulu -Natal, Durban, South Africa
Rheumatic heart disease	WT	The RHDGen Network: genetics of rheumatic heart disease and molecular epidemiology of <i>Streptococcus pyogenes</i> pharyngitis	Bongani Mayosi	University of Cape Town, South Africa

H3Africa, Human Heredity and Health in Africa; HIV, human immunodeficiency virus; NHLS, National Health Laboratory Service; NIH, National Institutes of Health; TB, tuberculosis; WT, Wellcome Trust.