



Africans Genomic Study: the Next Frontier of Global Genetic Medicine

Ambroise Wonkam, MD, PhD

Professor, and GeneMAP Director

Chair, H3Africa

Three reasons to study African Genomic Variations

1- Ancestral

2- Ecological

3- Equity

Ancestral African Genomes and complex trait

Missing Data in the Human Reference Genome

Assembly of a pan-genome from deep sequencing of 910 humans of African descent

Rachel M. Sherman^{1,2,*}, Juliet Forman^{1,3}, Valentin Antonescu¹, Daniela Puiu¹, Michelle

African pan-genome contains ~10% more DNA than the current human reference genome.

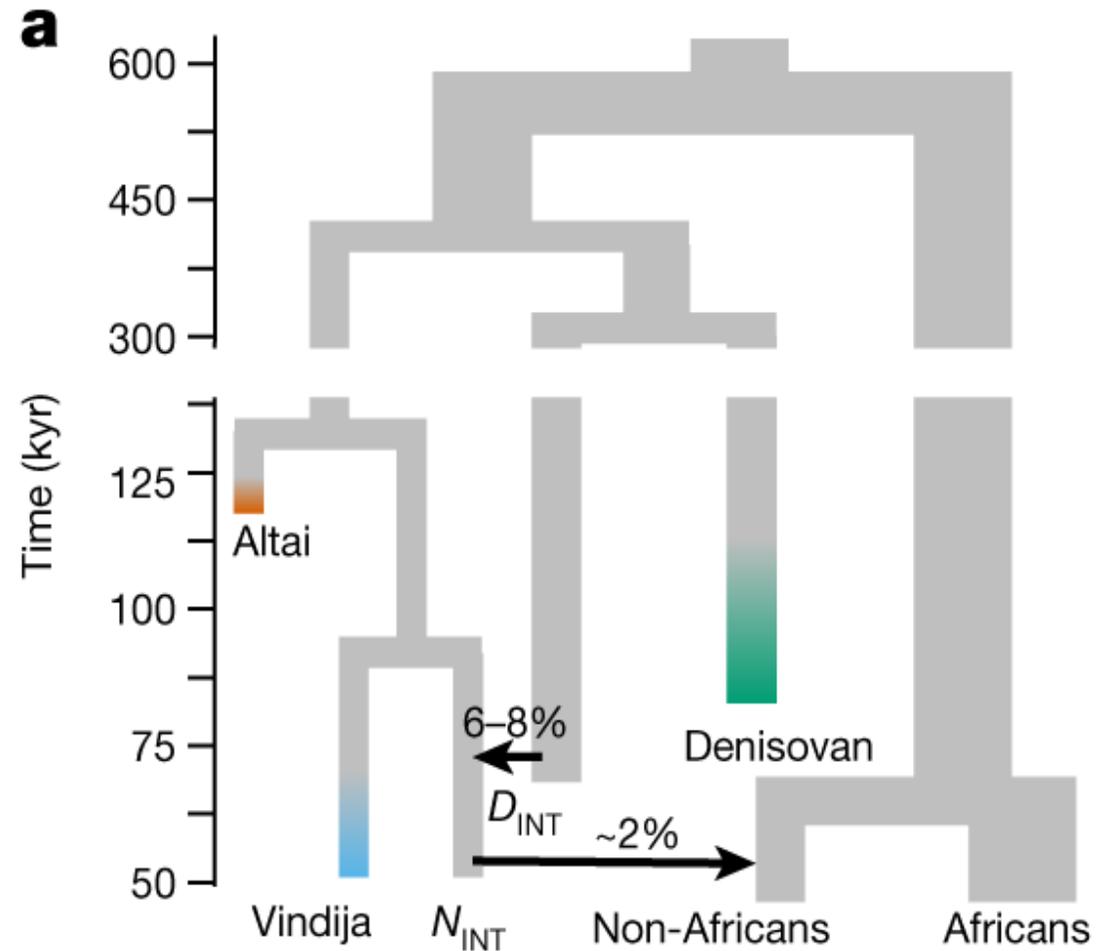
Nat Genet. 2019 January ; 51(1): 30–35. doi:10.1038/s41588-018-0273-y.

By underestimating human genetic diversity, we have been hampering scientific/medical progress...

Unknown Archaic human DNA in Africans

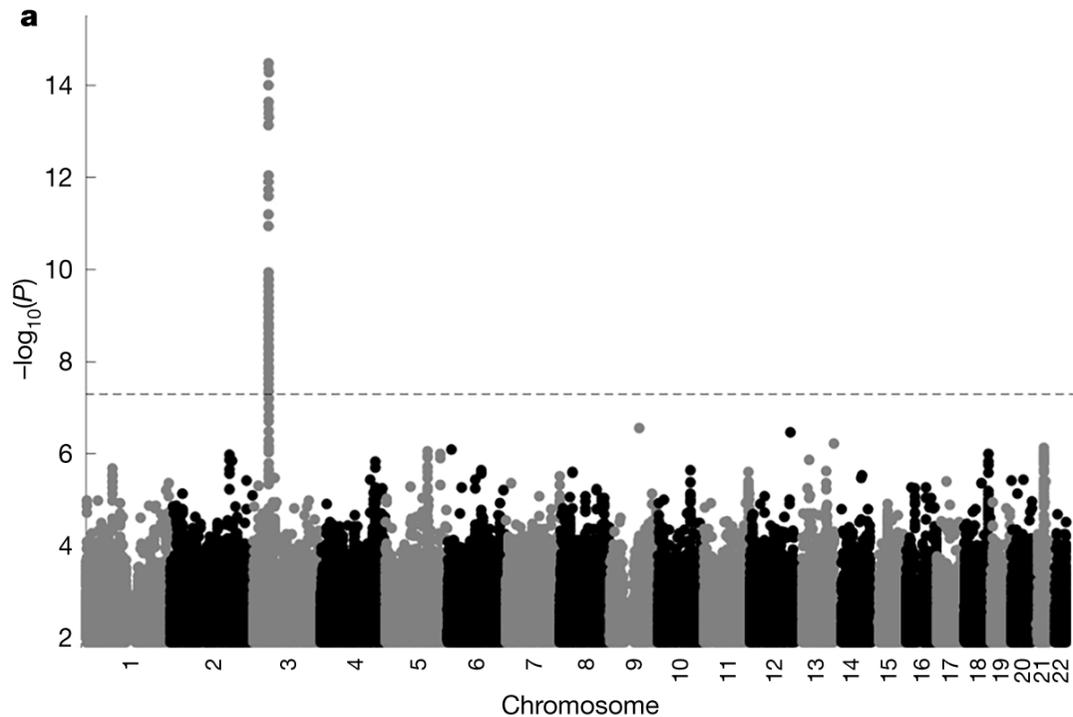


Homo Naledi



Archaic Human DNA, Health and Diseases

Neanderthal DNA and Covid -19



Others associated traits and diseases

- Dermatological phenotypes
- Neuro-psychiatric disorders
- Immunological functions

- Major genetic risk factor for severe COVID-19

[Zeberg & Pääbo](#) , Nature, 2020 Nov;587(7835):610-612

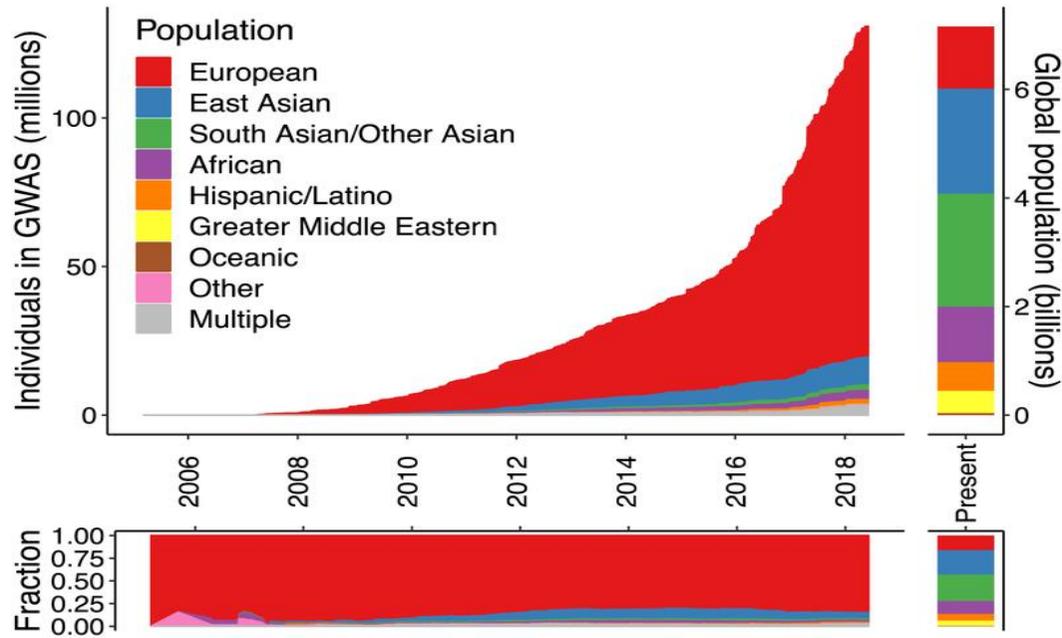
[Skov, L. et al.](#) *Nature*. **582**, 78-83, (2020)

[Almarri et al.](#) *Cell* 2020, 182, 1–11

[Dannemann & Kelso.](#) *Am J Hum Genet.* 2017; 101: 578–5

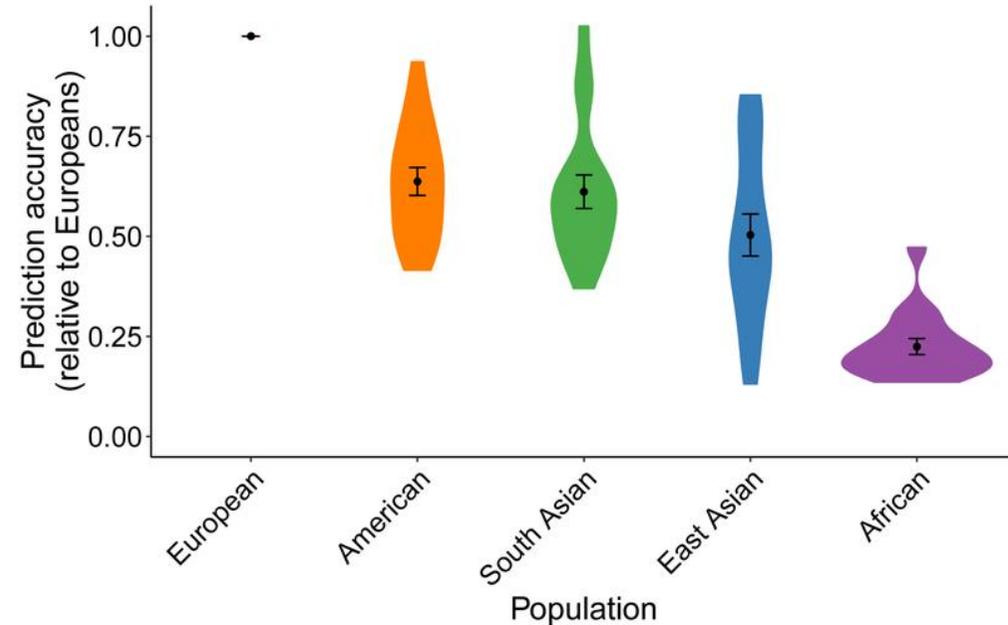
[Simonti et al.,](#) *Science* 2016 351, 6274: 737-741

Only 2.5% Africans for GWAS participants



Ancestry of GWAS participants over time compared to the global population

Underperformance of PRS in Africans

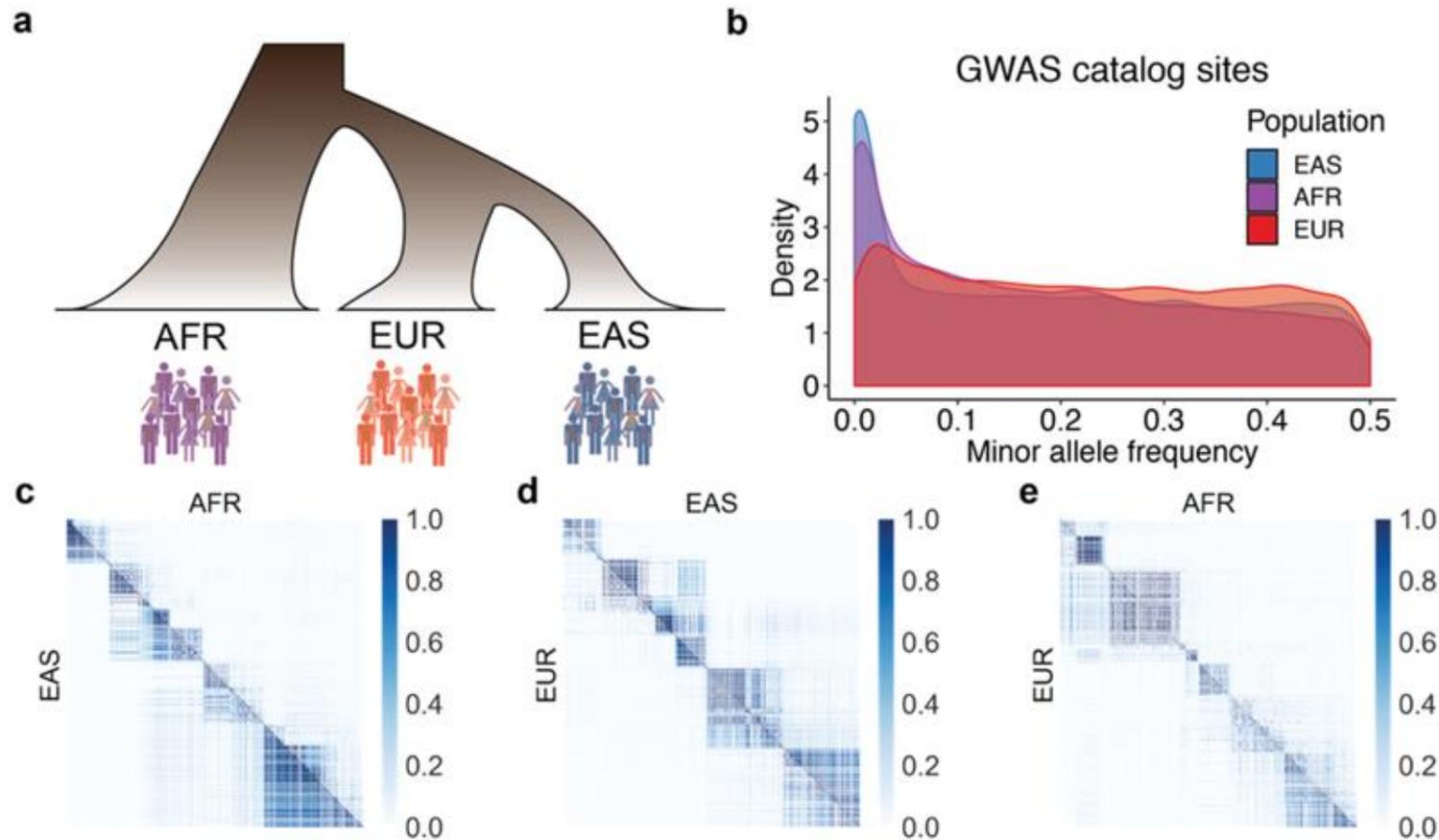


Amrtin et al. Nat Genet . 2019 April ; 51(4): 584–591.

Dikilitas et al. AJHG 2020, 106: 707-716

Lambert et al, Hum Mol Genet, 2019, 28: R133–R142

Lower LD in Africans Improve fine Mapping



Only 2.4% in GWAS studies are Africans but account for 7% associations

Gurdasani, D. *et al. Cell* **179**, 984-1002.e36, (2019).

Gurdasani, D. *et al. Nat Rev Genet* **20**, 520-535, (2019).

Amrtin et al. *Nat Genet* . 2019 April ; 51(4): 584–591.

Some Variants are more frequent in Africans

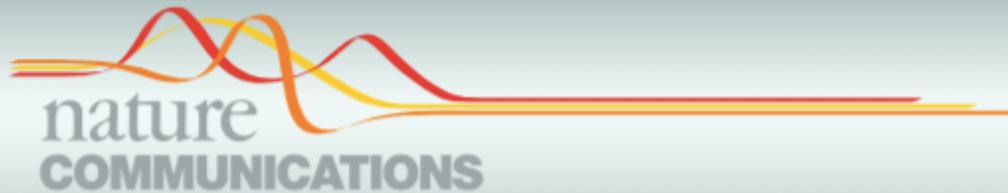
PCSK9: Frequent nonsense mutations *and* Low LDL cholesterol in Africans

- Mutations were common in African Americans (average 2%)

but rare in European Americans (<0.1%)

- Associated with a 40% reduction in plasma levels of LDL cholesterol
- ***PCSK9***: privileged target for dyslipidaemias therapeutics

Some Variants are Specific to Africans



ARTICLE

<https://doi.org/10.1038/s41467-019-10967-7>

OPEN

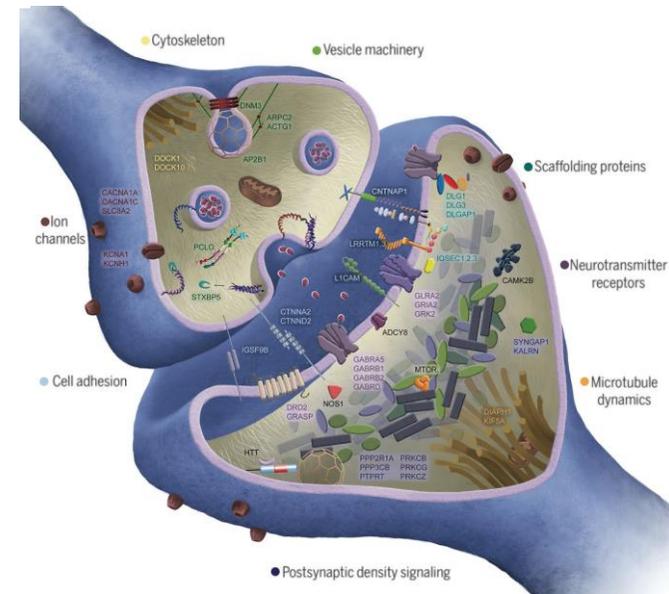
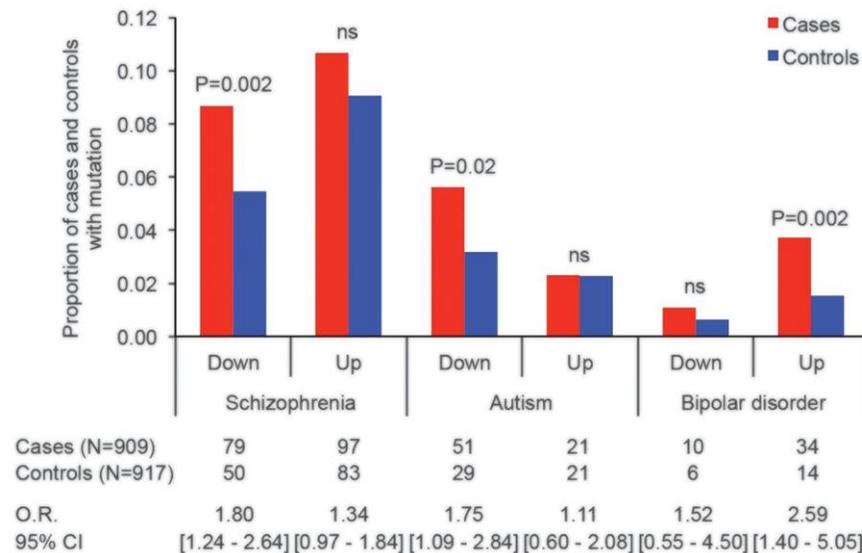
ZRANB3 is an African-specific type 2 diabetes locus associated with beta-cell mass and insulin response

Adebowale A. Adeyemo ^{1,22}, Norann A. Zaghoul^{2,3,22}, Guanjie Chen ¹, Ayo P. Doumatey¹, Carmen C. Leitch², Timothy L. Hostalley², Jessica E. Nesmith², Jie Zhou¹, Amy R. Bentley ¹, Daniel Shriner¹, Olufemi Fasanmade⁴, Godfrey Okafor⁵, Benjamin Eghan Jr⁶, Kofi Agyenim-Boateng⁶, Settara Chandrasekharappa⁷, Jokotade Adeleye⁸, William Balogun⁸, Samuel Owusu⁹, Albert Amoah⁹, Joseph Acheampong⁶, Thomas Johnson⁴, Johnnie Oli⁵, Clement Adebamowo¹⁰, South Africa Zulu Type 2 Diabetes Case-Control Study, Francis Collins¹², Georgia Dunston¹³ & Charles N. Rotimi ¹

Lower Samples Size Yields Larger Effect Sizes in Africans

Genetics of schizophrenia in the South African Xhosa

S. Gulsuner¹, D. J. Stein², E. S. Susser^{3,4}, G. Sibeko², A. Pretorius², T. Walsh¹, L. Majara⁵,



- Rare damaging mutations in multiple genes in ~ 1000 African
- Replicated in a Swedish cohort of 5000 cases.
- Africans yielded larger effect sizes

Gulsuner *et al.*, *Science* 367, 569–573 (2020)

Wonkam. *Nat Rev Genet.* 2022 Apr 14.

Ancestral African Genomes allelic and locus heterogeneity

Common and Founder Mutations for Monogenic Traits in Sub-Saharan African Populations

Amanda Krause,¹ Heather Seymour,¹
and Michèle Ramsay^{1,2}

- **Huntington disease**

Africans : triplet expansion mutations in *HTT* or *JPH3* in 67% and 33%

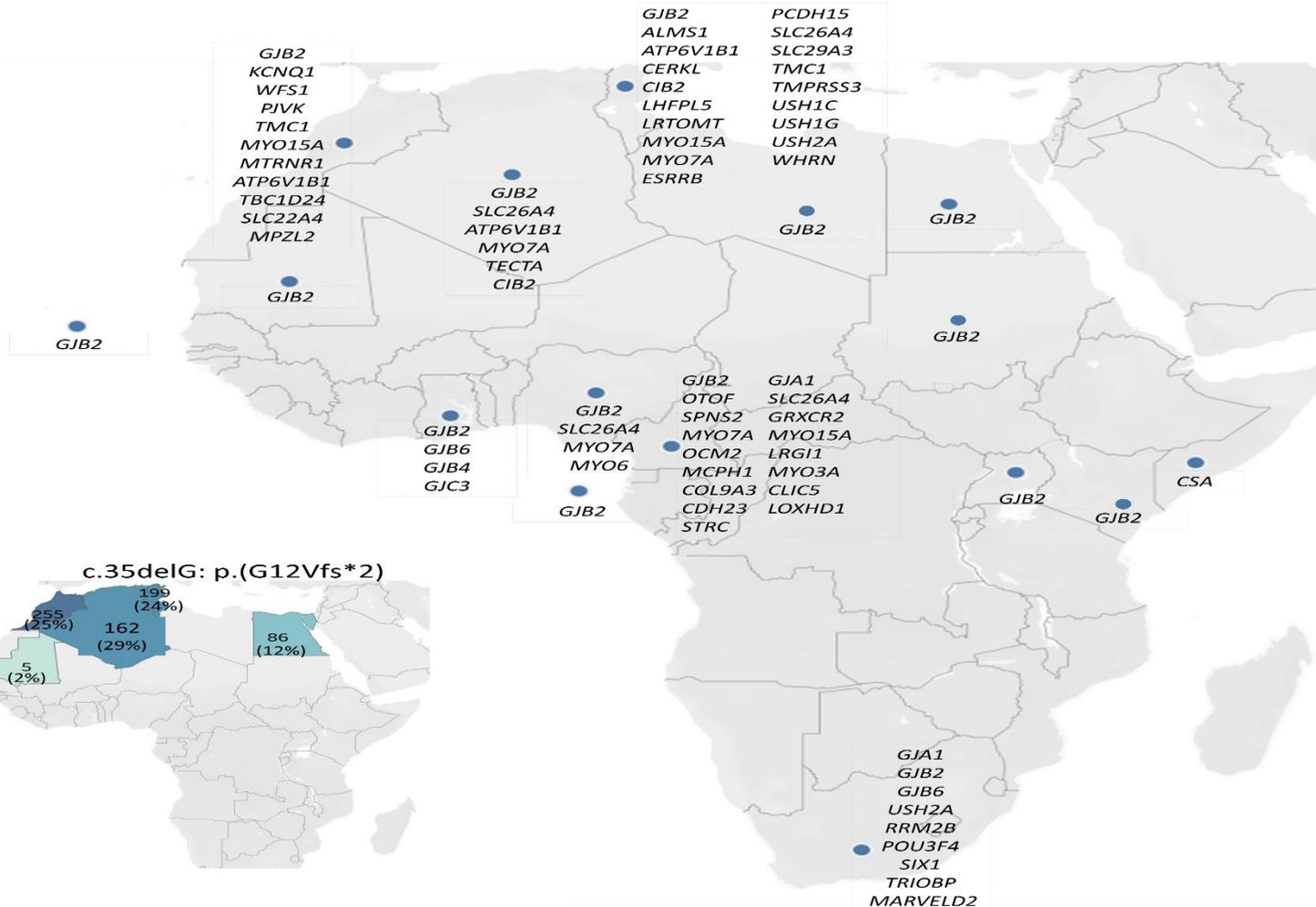
Europeans: 99% expansion in *HTT*

- **Cystic fibrosis**

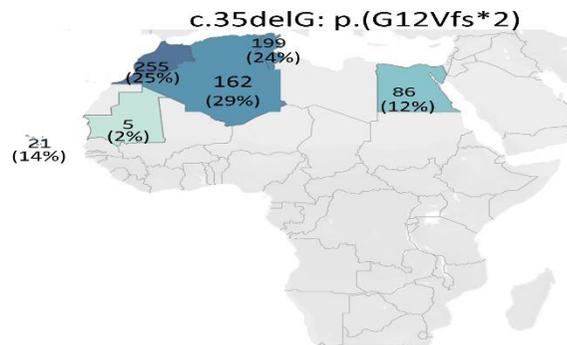
CFTR 3120+1G>A variant that is the most common causal t in African CF patients

GJB2 is not associated with Hearing loss in most Africans

A



B



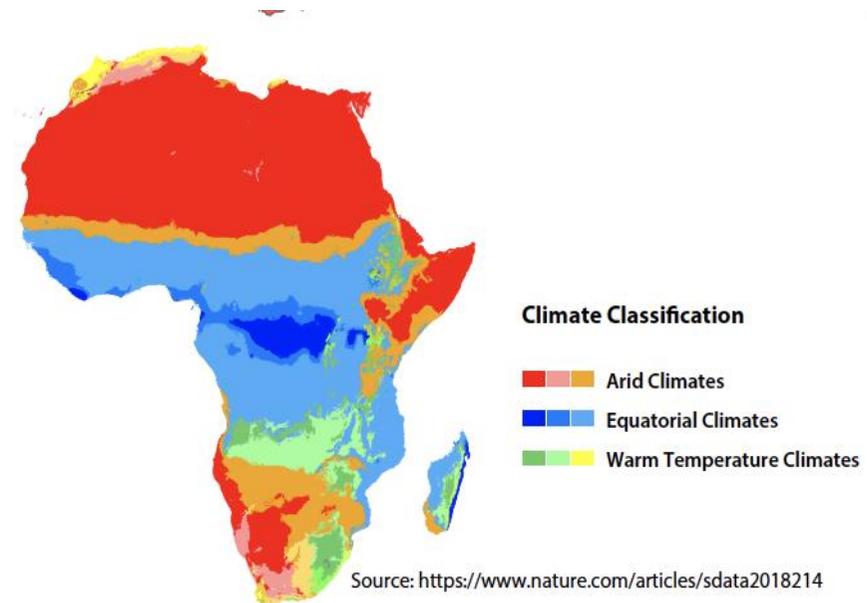
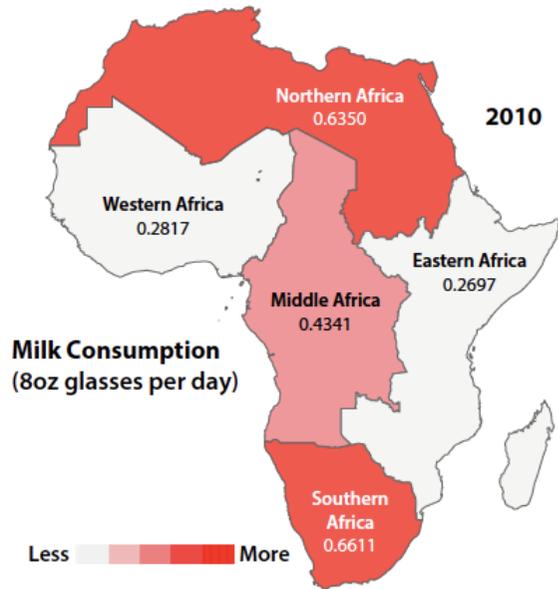
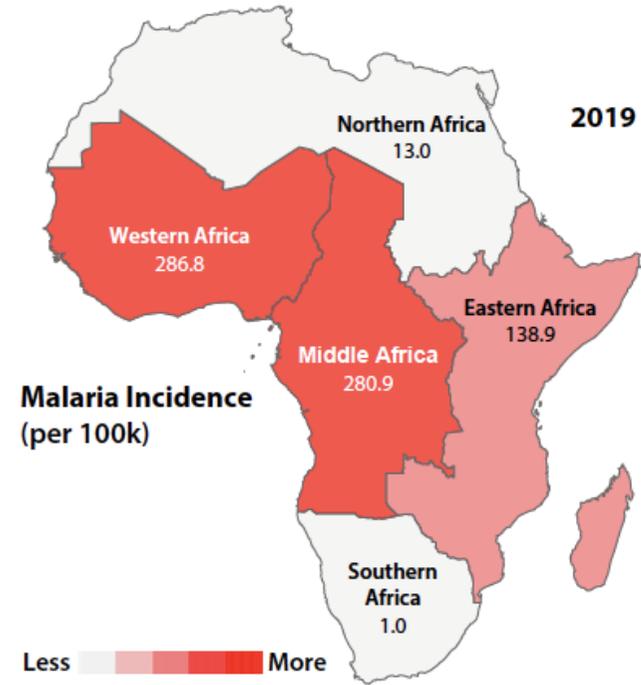
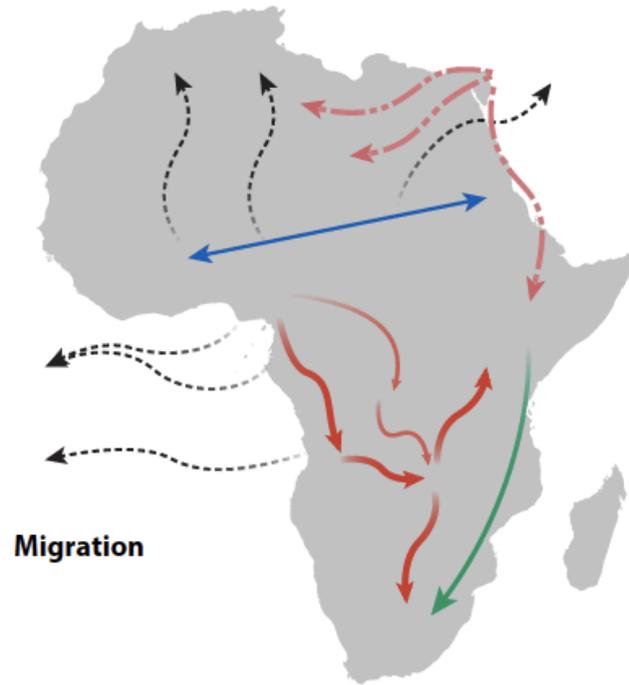
Hearing loss in Africa: current genetic profile

Samuel Mawuli Adadey^{1,2} · Edmond Wonkam-Tingang² · Elvis Twumasi Aboagye¹ · Osbourne Quaye¹ · Gordon A. Awandare¹ · Ambroise Wonkam²

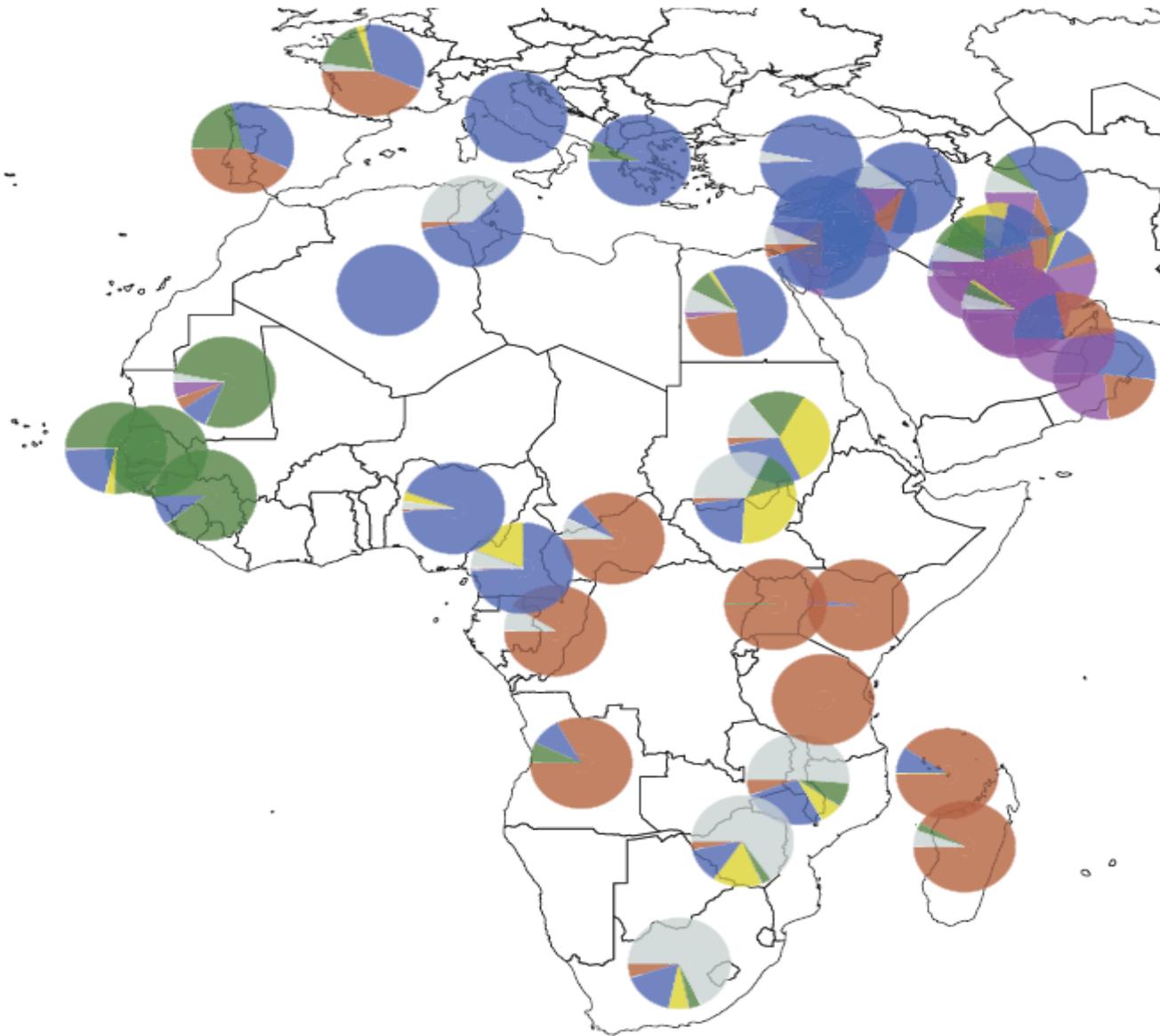
African Ecology

Adaptation signals in African genomes

Africa Genetic Diversity



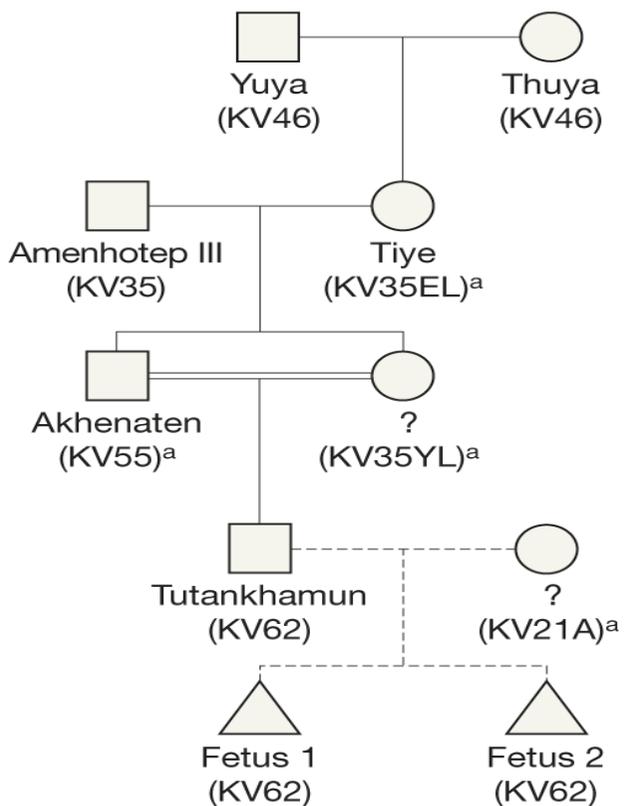
SCD haplotypes: single origin of S-mutation?



Distribution of mutated *HBB* gene cluster haplotypes in regional variants

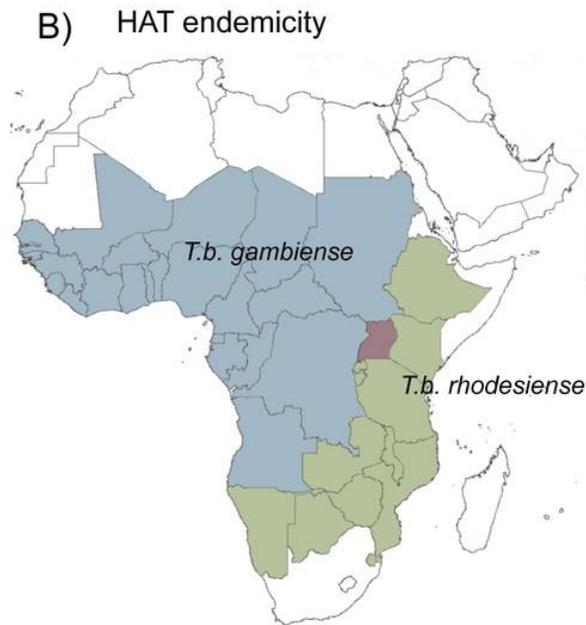
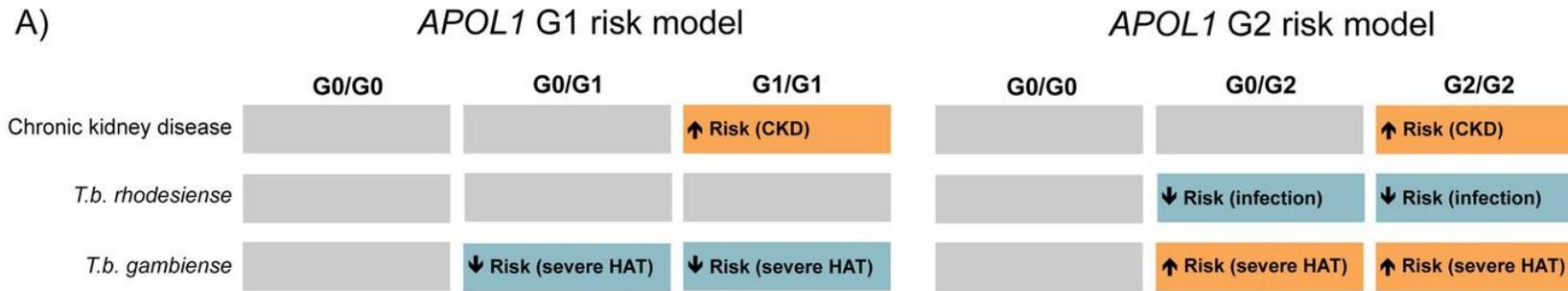
ARTICLE

Tutankhamun had Sickle Cell Disease?

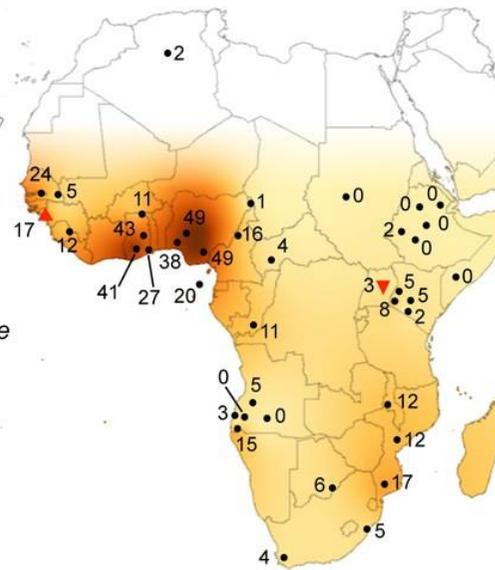


Hawass *et al.* *JAMA*. 2010 Feb 17;303(7):638-47.
 Timmann & Meyer *JAMA*. 2010 Jun 23;303(24):2473

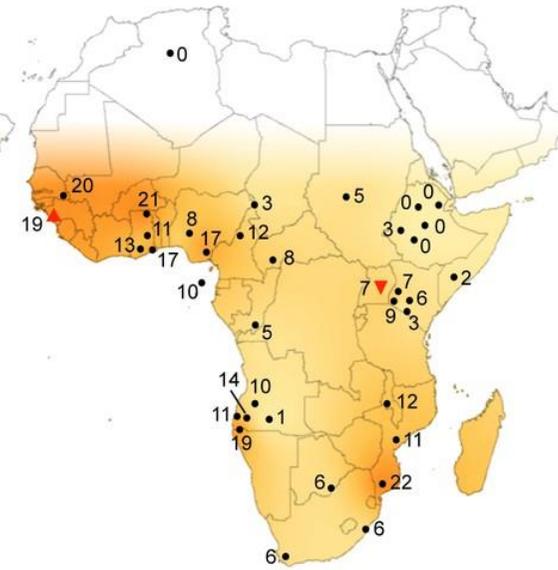
Trypanosomes and APOL1



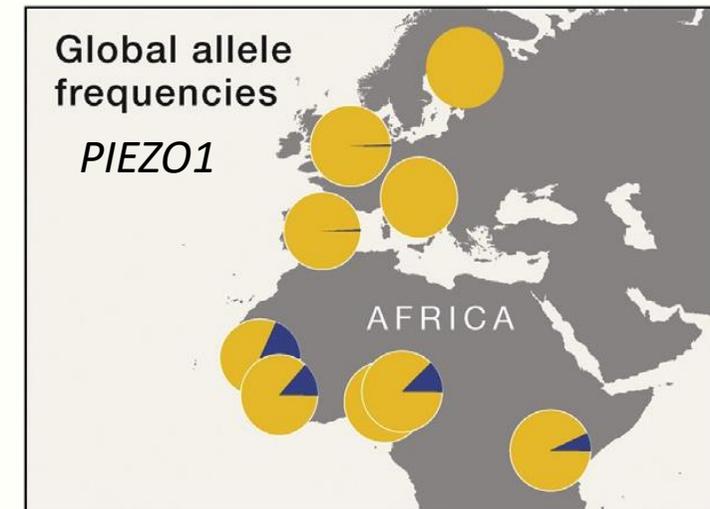
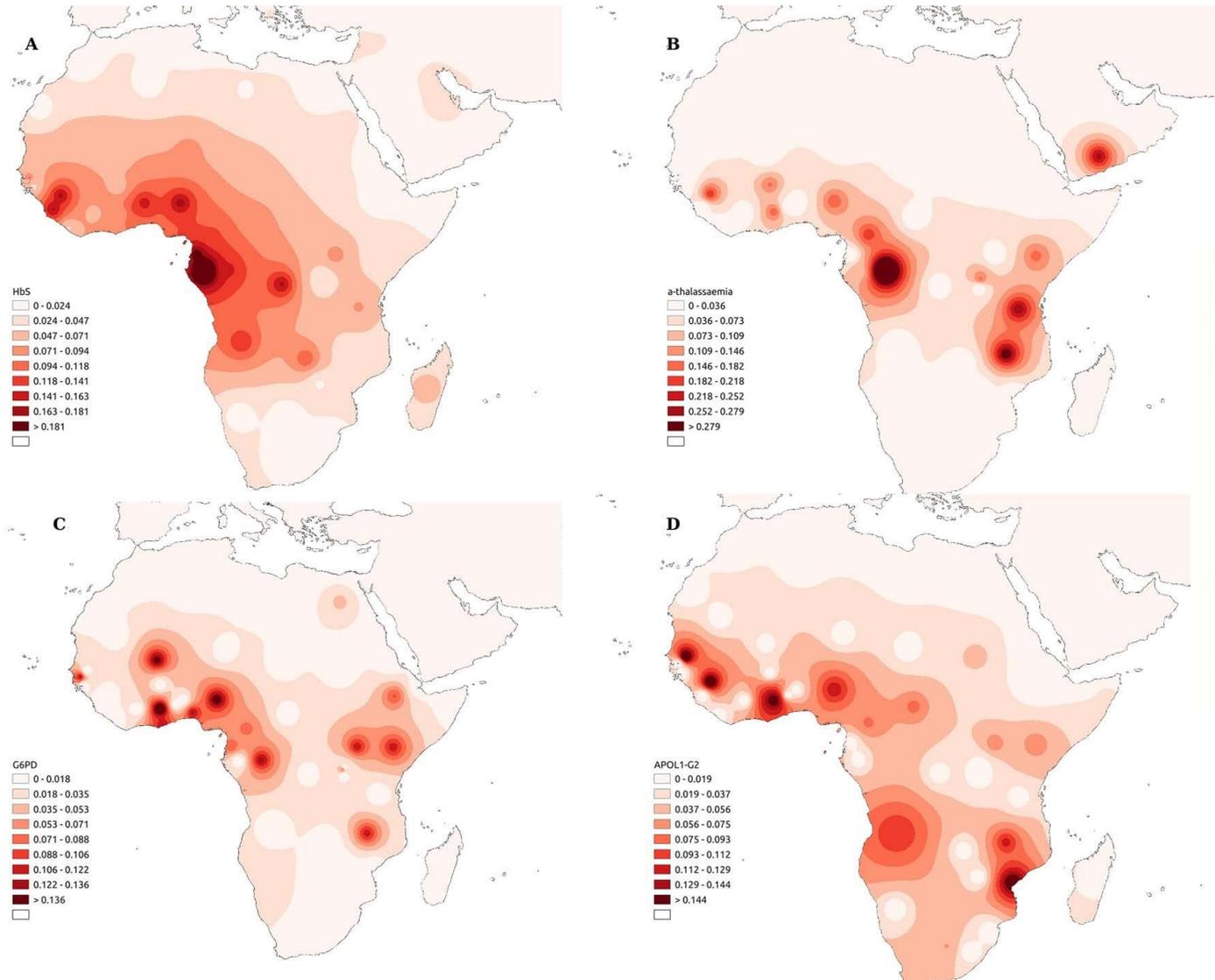
C) *APOL1* G1 allele distribution



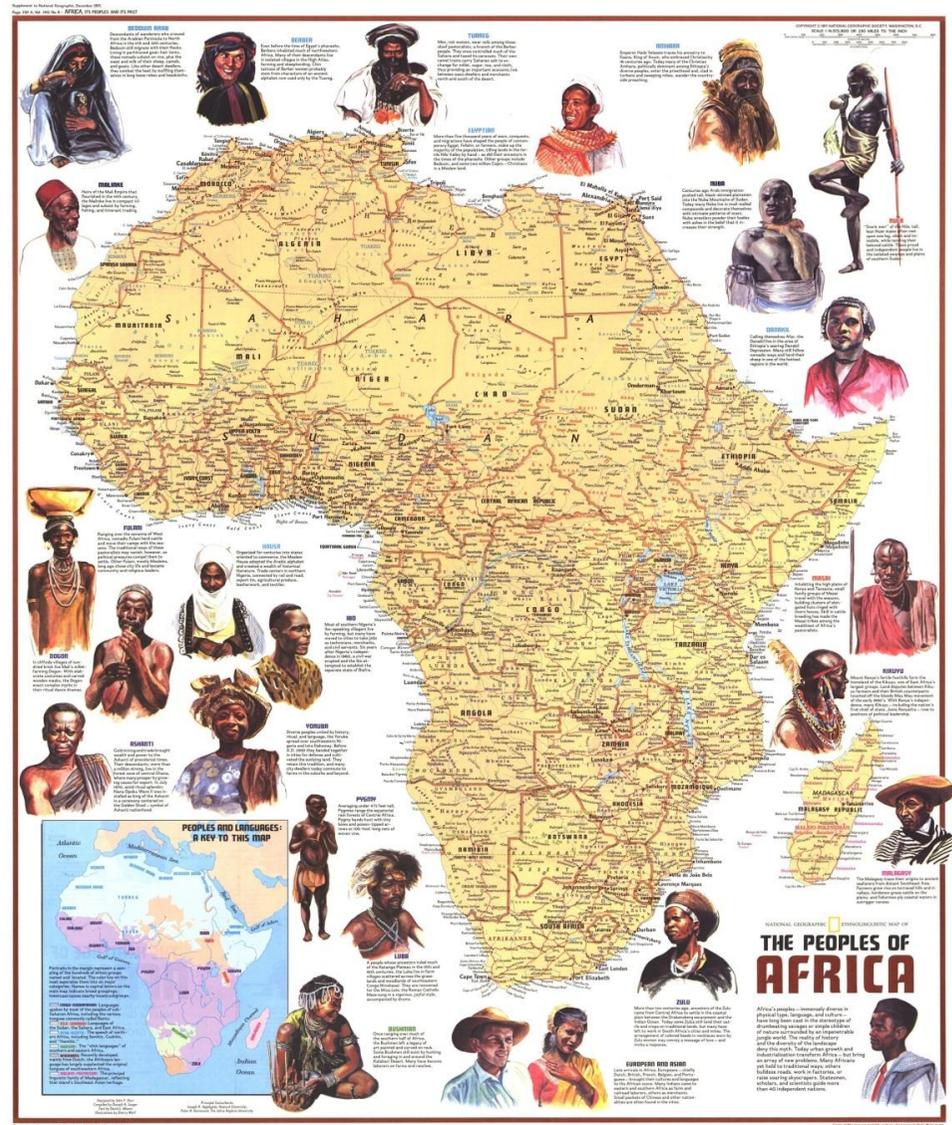
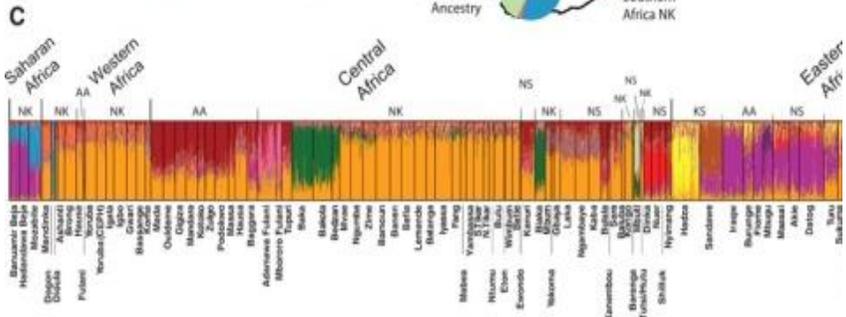
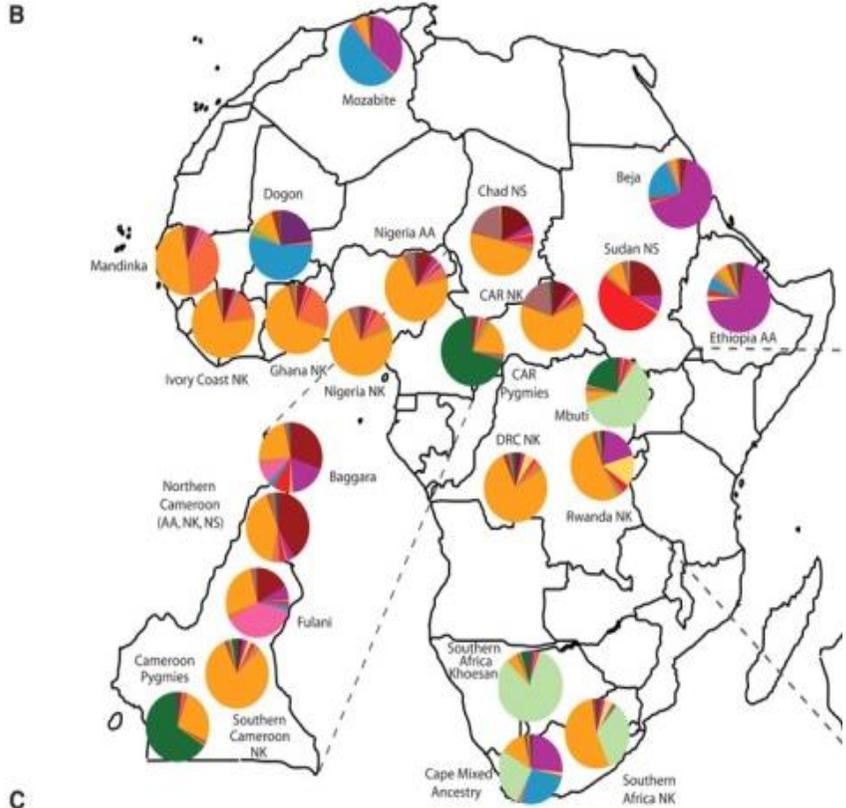
D) *APOL1* G2 allele distribution



Co-evolution of the *HBB*- β^S variant and other malaria, and trypanosome associated genes variant in ...

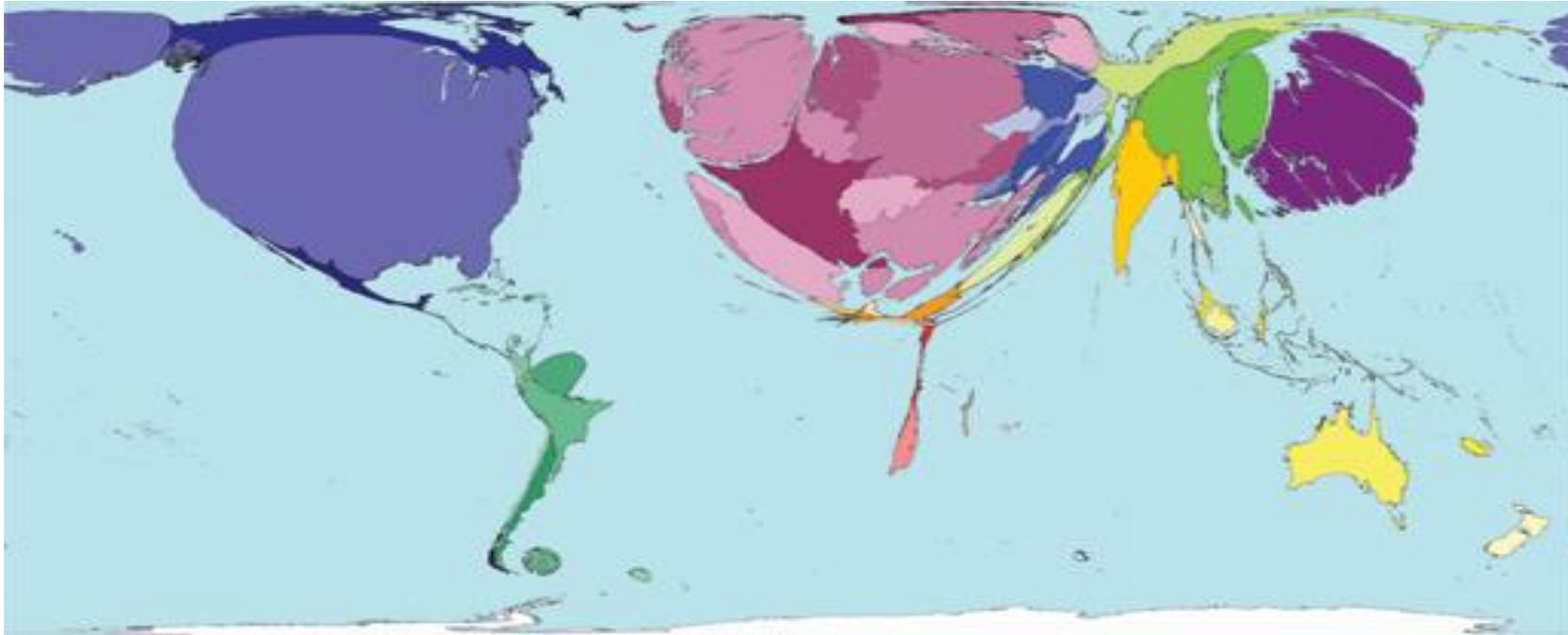


African Genetic Diversity



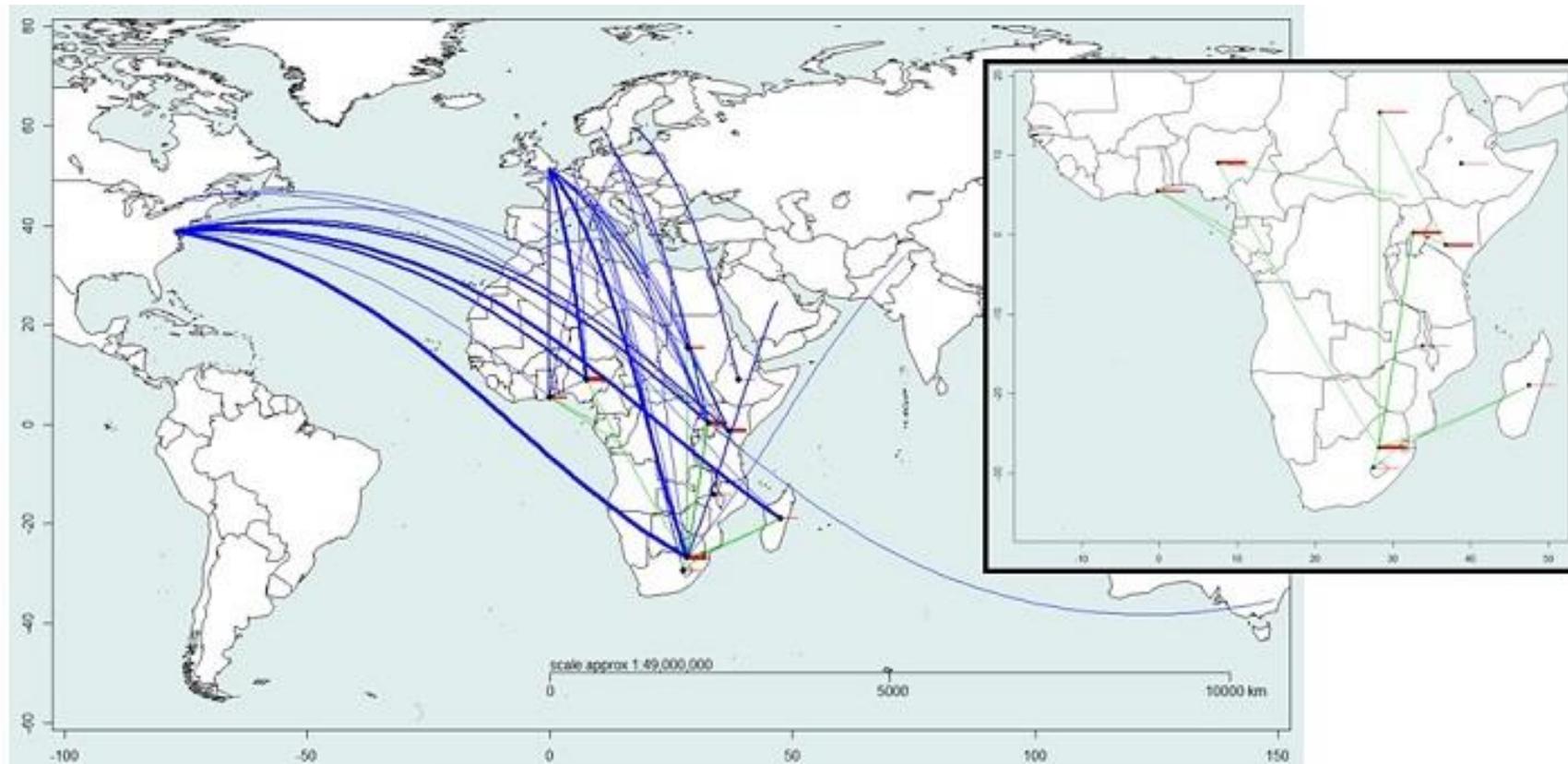
The Equity Imperative

Innovation & Wealth creation



- Africa is home to 15% of the world's population
- 5% of the world's gross domestic product (GDP)
- 1.3% of global investment in research and development
- **300000 of Human genomic history**

Bibliometric Trends of Health Economic Evaluation in Africa

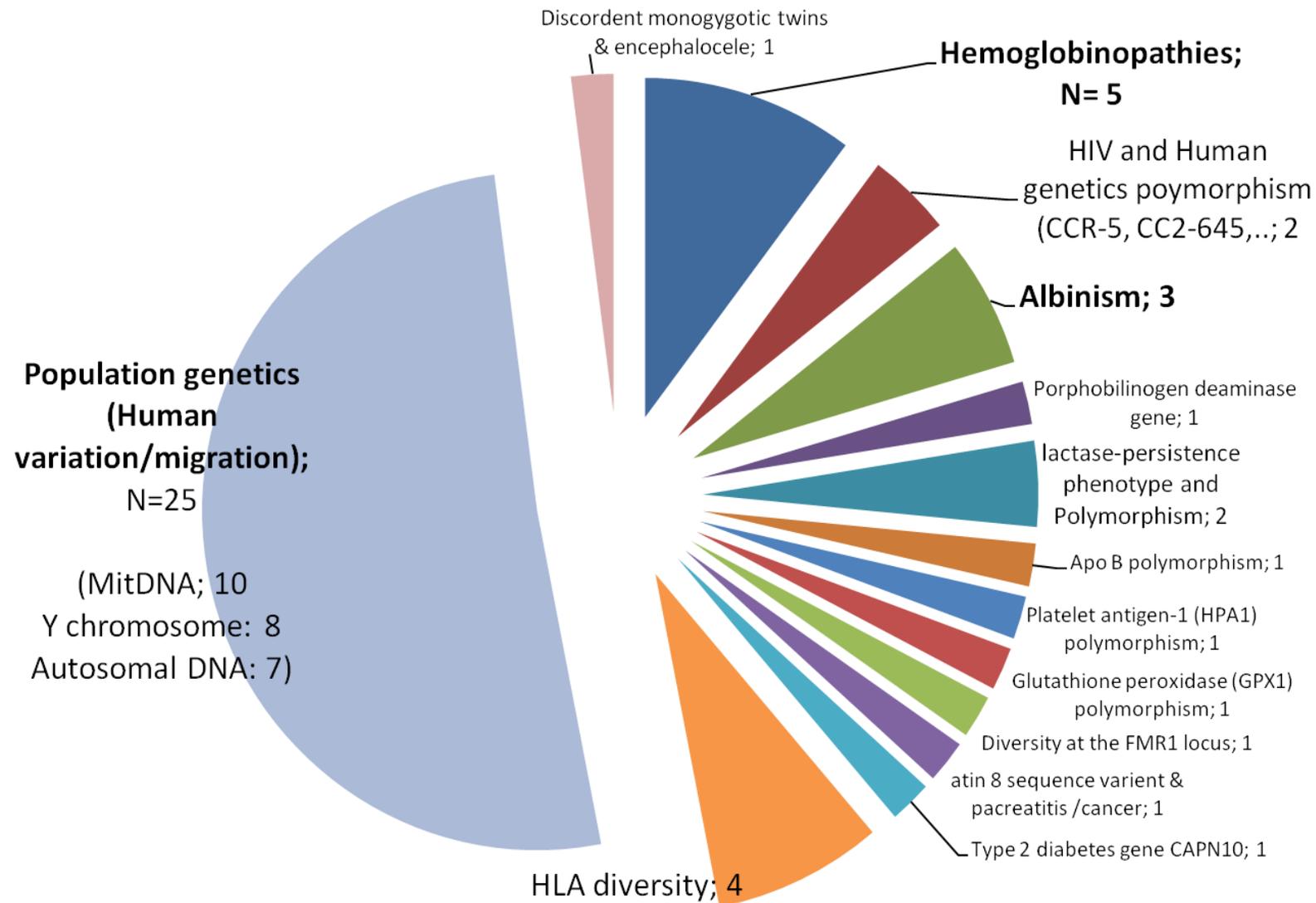


Blue lines: connections with authors outside Africa
Green lines: connections with authors of other African countries
Red lines: connections with authors of the same African country
The thickness of the line reflects the number of relationships
Source: Authors' Elaboration

health technology assessment (HTA)

2016 HTAi conference in Tokyo, May 2016

Existing issues : Research interest Bias



ELSI and African Genomics Research

Returning incidental findings in African genomics research

Ancestral and geographical issues underlie the need to develop Africa-specific guidelines for the return of genomics research results in Africa. In this Commentary, we outline the challenges that will inform policies and practices in the future.

Ambroise Wonkam and Jantina de Vries

Nature genetics 2020 52 (1), 17-20

Stigma in African genomics research: Gendered blame, polygamy, ancestry and disease causal beliefs impact on the risk of harm

Jantina de Vries^{a,*}, Guida Landouré^{b,c}, Ambroise Wonkam^{a,d,e}

Social Science & Medicine 258 (2020) 113091



H3Africa

Human Heredity and Health In Africa

H3Africa: African Populations Structures

Article

High-depth African genomes inform human migration and health

<https://doi.org/10.1038/s41586-020-2859-7>

Received: 10 May 2019

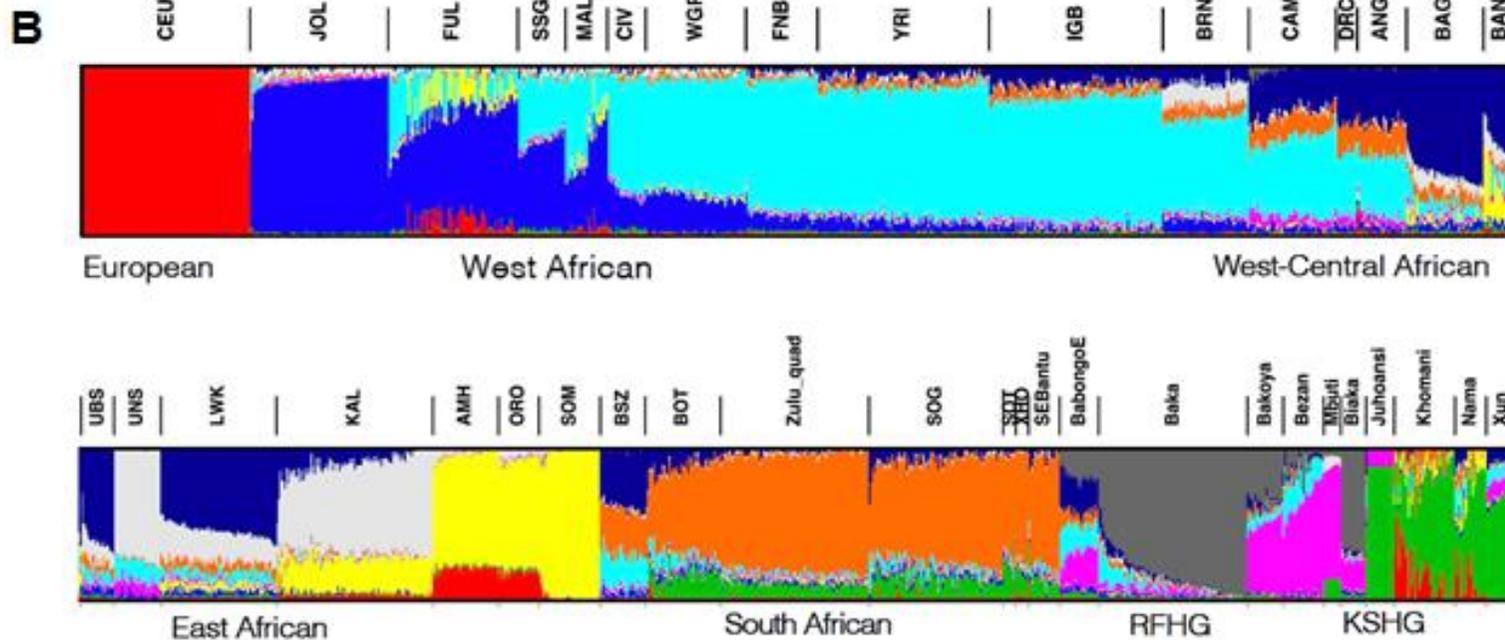
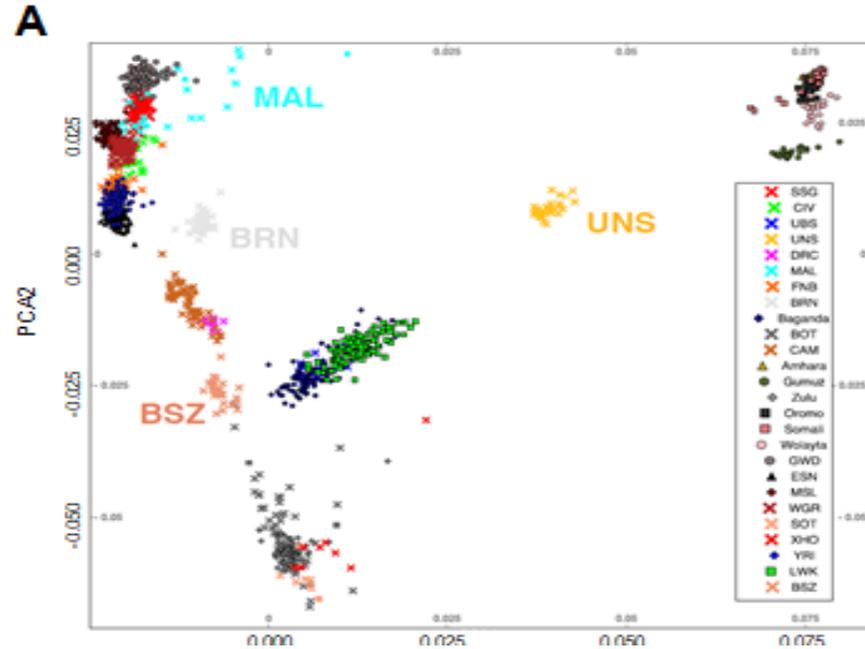
Accepted: 7 August 2020

Published online: 28 October 2020

Open access

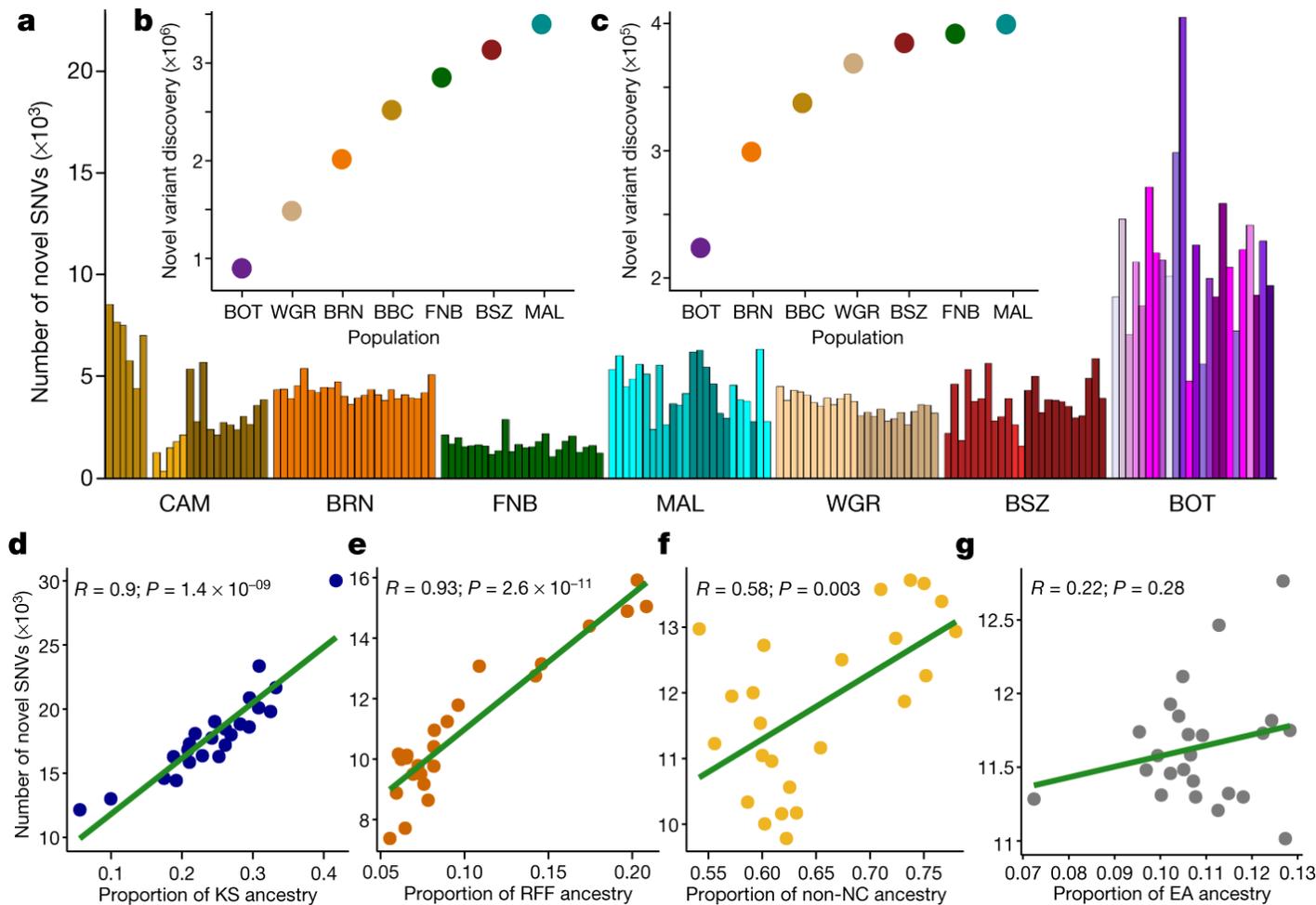
Check for updates

Ananyo Choudhury¹, Shaun Aron¹, Laura R. Botigue², Dhriti Sengupta³, Gerrit Botha⁴, Taoufik Bensellak⁵, Gordon Wells^{6,7}, Judit Kumuthin^{8,9}, Daniel Shriner¹⁰, Yasmina J. Fakim¹¹, Anisah W. Ghoorah¹², Eileen Dareng^{13,14}, Trust Odia¹⁵, Oluwadamilare Falola¹⁶, Ezekiel Adebisi^{17,18}, Scott Hazelhurst^{19,20}, Gaston Mazandu²¹, Oscar A. Nyangiri²², Mamama Mbiyavanga²³, Alta Benkahlal²⁴, Samar K. Kassim²⁵, Nicola Mulder²⁶, Sally N. Adebamowo^{27,28}, Emile R. Chimusa²⁹, Donna Muzny³⁰, Ginger Metcal³¹, Richard A. Gibbs^{32,33}, TrypanoGEN Research Group³⁴, Charles Rotimi³⁵, Michèle Ramsay^{36,37}, H3Africa Consortium³⁸, Adebowale A. Adeyemo³⁹, Zané Lombard^{40,41} & Neil A. Hanchard^{42,43}



Missing Data in the Human Reference Genome

H3Africa dataset: 3.4 million SNVs Novel variation

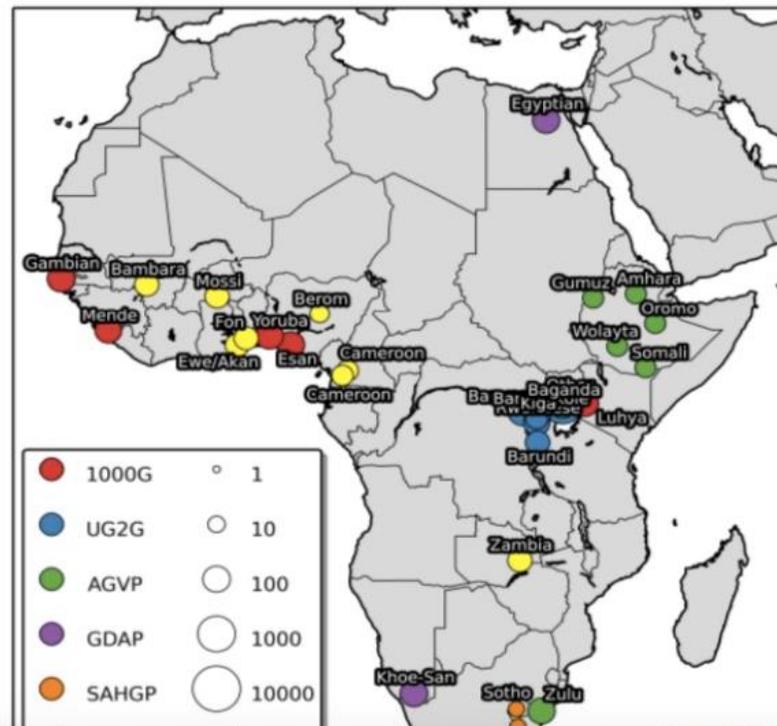


H3Africa CHIP Design



Sample size and distribution

| Source | Number of samples |
|------------|-------------------|
| GDAP | 204 |
| UG2G | 2000 |
| AGVP | 320 |
| 1000G | 507 |
| TrypanoGEN | 212 |
| Baylor | 348 |
| SAHGP | 16 |
| Total | 3607 |



2.5M SNPs, 700'000 selected from GWAS data from SSA

H3A Array, trait and disease

ORIGINAL RESEARCH



Classical Cardiovascular Risk Factors and HIV are Associated With Carotid Intima-Media Thickness in Adults From Sub-Saharan Africa: Findings From H3Africa AWI-Gen Study

Engelbert A. Nonterah, MBChB, MSc; Palwende R. Boua, MSc; Kerstin Klipstein-Grobusch, PhD; Gershim Asiki, MBChB, PhD; Lisa K. Micklesfield, PhD; Godfred Agongo, MPhil; Stuart A. Ali, PhD; Felistas Mashinya, PhD; Herman Sorgho, PhD; Seydou Nakanabo-Diallo, MBChB, MSc; Cornelius Debpur, PhD; Catherine Kyobutungi, MBChB, PhD; Marianne Alberts, PhD; Shane Norris, PhD; Stephen Tollman, MBChB, PhD; Halidou Tinto, PhD; Cassandra C. Soo, MSc; Freedom Mukomana, MSc; Scott Hazelhurst, PhD; Alisha N. Wade, MBBS, DPhil; Kathleen Kahn, MBChB, PhD; Abraham R. Oduro, MBChB, PhD; Diederick E. Grobbee, MD, PhD; Osman Sankoh, PhD; Michèle Ramsay, PhD; Michiel L. Bots, MD, PhD; Nigel J. Crowther, PhD; members and contributors of AWI-Gen and the H3Africa Consortium

Cell

Uganda Genome Resource Enables Insights into Population History and Genomic Discovery in Africa

Graphical Abstract

Authors

Deepti Gurdasani, Tommv Carstensen.

Resource

Whole-Exome Sequencing Reveals Uncaptured Variation and Distinct Ancestry in the Southern African Population of Botswana

Gaone Retshabile,¹ Busisiwe C. Mlotshwa,¹ Lesedi Williams,¹ Savannah Mwesigwa,² Gerald Mboowa,² Zhuoyi Huang,⁴ Navin Rustagi,⁴ Shanker Swaminathan,^{5,6} Eric Katagiriya,² Samuel Kyobe,² Misaki Wayengera,³ Grace P. Kisitua,⁷ David P. Kateete,^{2,3} Eddie M. Wampande,^{2,8} Koketso Maplanka,¹ Ishmael Kasvosve,⁹ Edward D. Pettitt,¹⁰ Mogomotsi Matshaba,^{10,11} Betty Nsangi,⁷ Marape Marape,¹⁰ Masego Tsimako-Johnstone,¹ Chester W. Brown,^{5,12} Fuli Yu,^{4,5} Adeodata Kekitiinwa,^{7,11} Moses Joloba, Sununguko W. Mpoloka,¹ Graeme Mardon,^{5,13} Gabriel Anabwani,^{10,11} Neil A. Hanchard,^{5,6,*} and for the Collaborative African Genomics Network (CAfGEN) of the H3Africa Consortium



ARTICLE



<https://doi.org/10.1038/s41467-021-22207-y>

OPEN

Genetic substructure and complex demographic history of South African Bantu speakers

Dhriti Sengupta^{1,15}, Ananyo Choudhury^{1,15}, Cesar Fortes-Lima², Shaun Aron¹, Gavin Whitelaw^{3,4}, Koen Bostoen⁵, Hilde Gunnink⁵, Natalia Chousou-Polydouri⁶, Peter Delius⁷, Stephen Tollman⁸, F. Xavier Gómez-Olivé⁸, Shane Norris⁹, Felistas Mashinya¹⁰, Marianne Alberts¹⁰, AWI-Gen Study*, H3Africa Consortium*, Scott Hazelhurst¹¹, Carina M. Schlebusch^{2,13,14,16} & Michèle Ramsay^{1,12,16}

ASSOCIATION STUDIES ARTICLE

Discovery and fine-mapping of kidney function loci in first genome-wide association study in Africans

Segun Fatumo^{1,2,3,*}, Tinashe Chikowore^{4,5}, Robert Kalyesubula^{1,2,6}, Rebecca N. Nsubuga¹, Gershim Asiki⁹, Oyekanmi Nashiru³, Janet Seeley^{1,2}, Amelia C. Crampin², Dorothea Nitsch², Liam Smeeth², Pontiano Kaleebu¹, Stephen Burgess⁷, Moffat Nyirenda^{1,2}, Nora Franceschini⁸, Andrew P. Morris^{10,†}, Laurie Tomlinson^{2,†} and Robert Newton^{1,†}

ARTICLE

Kidney damage and associated risk factors in rural and urban sub-Saharan Africa (AWI-Gen): a cross-sectional population study



Jaya A George*, Jean-Tristan Brandenburg*, June Fabian, Nigel J Crowther, Godfred Agongo, Marianne Alberts, Stuart Ali, Gershim Asiki, Palwende R Boua, F Xavier Gómez-Olivé, Felistas Mashinya, Lisa Micklesfield, Shukri F Mohamed, Freedom Mukomana, Shane A Norris, Abraham R Oduro, Cassandra Soo, Hermann Sorgho, Alisha Wade, Saraladevi Naicker, Michèle Ramsay as members of AWI-Gen and the H3Africa Consortium



Summary

Background Rapid epidemiological health transitions occurring in vulnerable populations in Africa that have an existing burden of infectious and non-communicable diseases predict an increased risk and consequent prevalence of

Lancet Glob Health 2019; 7: e1632-43

Articles

Dominant modifiable risk factors for stroke in Ghana and Nigeria (SIREN): a case-control study



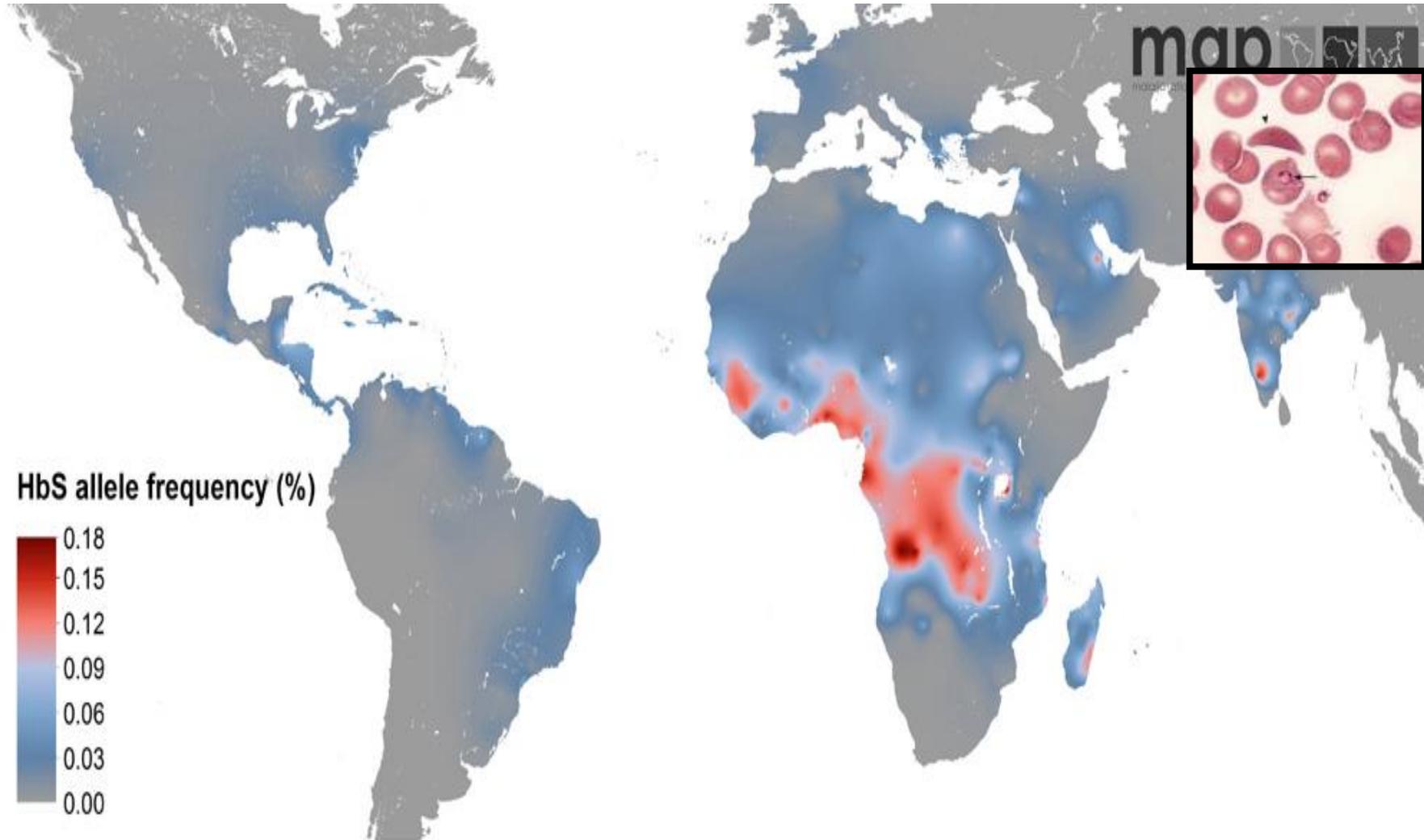
Mayowa O Owolabi, Fred Sarfo, Rufus Akinyemi, Mulugeta Gebregziabher, Onoja Akpa, Albert Akpaku, Kolawole Wahab, Reginald Obiako, Lukman Owolabi, Bruce Ovbiagele, on behalf of the SIREN Team* as part of H3Africa Consortium



Summary

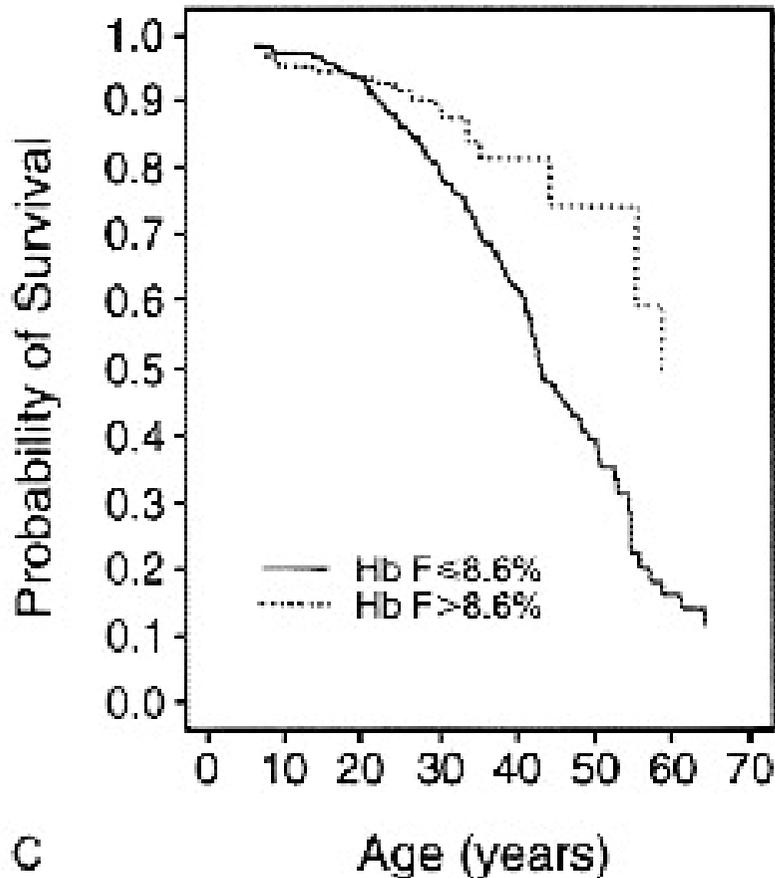
The Tragedy of the Common(s)...
Sickle Cell Disease

Global Burden of SCD



Burden of SCD in Africa
237, 253 births a year (76%)

SCD, and HbF, and survival



DNA polymorphisms at the *BCL11A*, *HBS1L-MYB*, and β -globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease

Guillaume Lettre^{1,2,5}, Vijay G. Sankaran^{3,4}, Marcos André C. Bezerra^{6,7}, Aderson S. Araújo^{6,7}, Manuela Uda⁸, Serena Sanna⁹, Antonio Cao¹⁰, David Schlessinger¹¹, Fernando F. Costa^{5,5}, Joel N. Hirschhorn^{1,5}, and Stuart H. Orkin^{5,11}

blood

2011 117: 1390-1392
Prepublished online November 10, 2010;
doi:10.1182/blood-2010-08-302703

Genetics of fetal hemoglobin in Tanzanian and British patients with sickle cell anemia

Julie Makani, Stephan Menzel, Siana Nkya, Sharon E. Cox, Emma Drasar, Deogratius Soka, Albert N. Komba, Josephine Mgaya, Helen Rooks, Nisha Vasavda, Gregory Fegan, Charles R. Newton, Martin Farrall and Swee Lay Thein

OPEN ACCESS Freely available online

PLOS ONE

Association of Variants at *BCL11A* and *HBS1L-MYB* with Hemoglobin F and Hospitalization Rates among Sickle Cell Patients in Cameroon

Ambrose Wonkam^{1*}, Valentina J. Ngo Bitoungui², Anna A. Vorster¹, Raj Ramesar^{1,3}, Richard S. Cooper⁴, Bamidele Tayo⁴, Guillaume Lettre⁵, Jeanne Ngogang²

N Engl J Med 1994;330:1639-44.

Gene Editing/Therapy for SCD

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Gene Therapy in a Patient with Sickle Cell Disease

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β -Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace,

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

JANUARY 21, 2021

VOL. 384 NO. 3

Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease

Erica B. Esrick, M.D., Leslie E. Lehmann, M.D., Alessandra Biffi, M.D., Ph.D., Maureen Achebe, M.D.,

The NEW ENGLAND
JOURNAL of MEDICINE

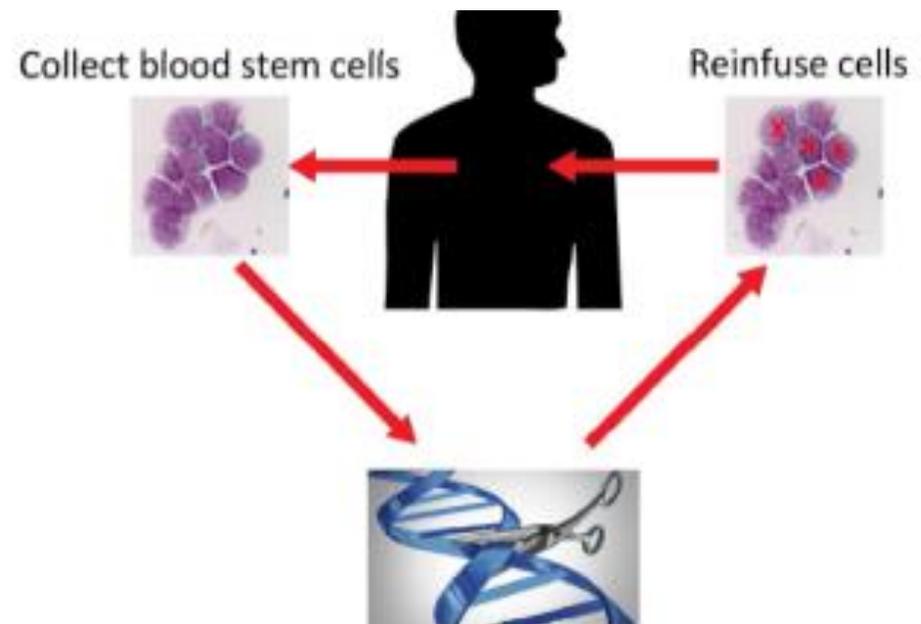
ESTABLISHED IN 1812

FEBRUARY 17, 2022

VOL. 386 NO. 7

Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

J. Kanter, M.C. Walters, L. Krishnamurti, M.Y. Mapara, J.L. Kwiatkowski, S. Rifkin-Zenenberg, B. Aygun, K.A. Kasow, F.J. Pierciey, Jr., M. Bonner, A. Miller, X. Zhang, J. Lynch, D. Kim, J.-A. Ribeil, M. Asmal, S. Goyal, A.A. Thompson, and J.F. Tisdale



N ENGL J MED 376;9 NEJM.ORG MARCH 2, 2017

N Engl J Med 2021;384:252-60.

N ENGL J MED 384;3 NEJM.ORG JANUARY 21, 2021

N Engl J Med 2022;386:617-28.

The genomic keys to sickle-cell therapy

Because it is caused by a single point genetic mutation, sickle-cell disease represents an ideal opportunity for gene and RNA therapy. Ambrose Wonkam lays out the promise and challenges ahead.

Although the first clinical case of sickle-cell disease was described 111 years ago, progress in drug development has been slow. Only two medications have been approved in the United States and Europe: hydroxyurea (HU) 20 years ago, and crizanlizumab more recently. Only HU is available in African countries. Limited clinical acceptance of the drugs provides further impetus for developing therapies.

Sickle-cell disease is the result of a single nucleotide substitution in the gene that codes for a protein involved in producing haemoglobin (Hb) – the protein that constitutes 70% of red blood cells and transports oxygen to all organs. In sickle-cell disease, the abnormal, sickled Hb (HbS) tends to polymerize in red blood cells. That process causes the cells to become deformed and to take on a sickle shape. Such cells are most often destroyed, leading to anaemia. In addition, sickled red blood cells tend to obstruct blood vessels, resulting in damage to multiple organs. In Africa, at least 50% of children with untreated sickle-cell disease die before the age of 5.

Because it is caused by a single point mutation, sickle-cell disease is an ideal target for gene therapy. There are two key ways to accelerate the development of curative therapies for the disease through genomics research. The first is to explore the missing heritability of fetal haemoglobin (HbF) in Africa: currently, 80% of gene variants accounting for heritability of HbF are still to be identified. In the womb, HbF is the dominant form of haemoglobin. After birth, the level of HbF decreases as adult haemoglobin A (HbA) replaces it.

The mechanism that controls the switch from HbF to HbA is dependent on specific variations in a few genes. Because the presence of HbF in red blood cells blocks HbS polymerization, interventions that allow individuals with the disease to continue to produce HbF can result in a longer life expectancy. The most common way to promote HbF production is to block proteins that inhibit HbF expression. One such option is inhibition of the gene that codes for the protein BCL11A, which modulates the switch from HbF to HbA at birth¹.

Variants already identified in HbF-modulating loci (for



“Sickle-cell disease is an ideal target for gene therapy.”

Ambrose Wonkam is a geneticist at the University of Cape Town in South Africa
e-mail: ambrose.wonkam@uct.ac.za

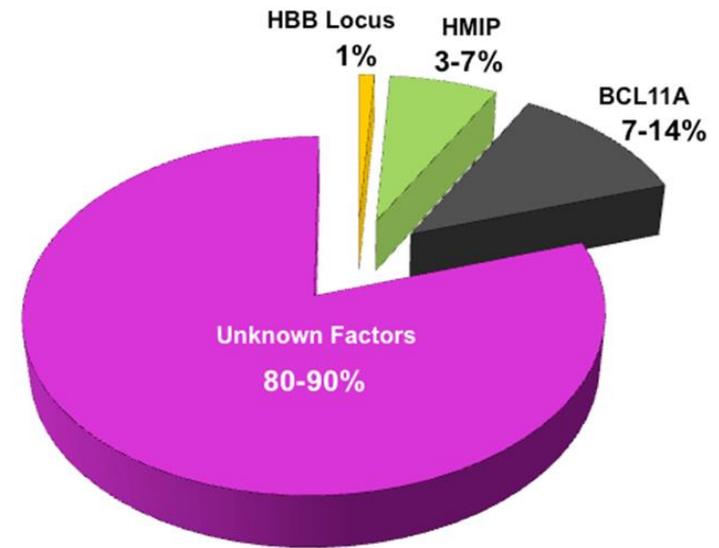
example, in BCL11A), however, explain no more than roughly 20% of HbF levels in African individuals with sickle-cell disease², compared with up to 50% of the variation in HbF in Europeans – possibly because other HbF-controlling loci or variations are yet to be discovered in Africans. The genome-wide association studies (GWAS) that discovered known modulators of HbF, such as BCL11A, were performed in populations of European ancestry³. These studies used GWAS arrays designed for that population and thus did not necessarily capture Africa's high genetic diversity.

Although people of African ancestry comprise only about 2.5% of GWAS participants globally, they account for nearly 8% of the trait and disease associations⁴. The high GWAS yields in the few studies that included Africans are due to the high genetic diversity in this group, the oldest of humanity's populations. With more than 300,000 years of human genomic evolutionary history in Africans, and only a small group of individuals having originally moved out of Africa (the ancestors of present-day Europeans and Asians), most of the human genome variations stayed behind. Consequently, millions of genetic variants, some of which are yet to be characterized, either occur more or less frequently in Africans or are specific to this population – which makes detailed identification of gene variants for disease or trait associations easier. Indeed, research to uncover the missing heritability of HbF-promoting loci in populations of African ancestry could provide druggable targets for effective promotion of HbF.

The second genetic approach to sickle-cell disease therapy involves RNA. Small non-coding RNAs called microRNAs (miRNAs) gum up the production of proteins by binding to the transcription machinery in a cell. They could be used to target the entire pathway of HbF production – particularly to suppress the expression of HbF-inhibitor proteins, such as BCL11A – which would have a much stronger effect than targeting a single gene. Research that identifies more candidate miRNAs that act on HbF production will provide an attractive route for future sickle-cell therapies that mimic HU-induced HbF production⁵. Mediation of HbA or HbF production through the injection of messenger RNA, a process used in COVID-19 vaccines, could provide another RNA-based technique for sickle-cell therapy.

Although the success and equitability of such genomic research is questionable, we can take encouragement from the faster-than-expected development of the COVID-19 vaccine. Such research should be accompanied by a mechanism, overseen by international agencies such as the World Health Organization, to ensure its benefits are equitably distributed, through the establishment of centres of excellence for sickle-cell disease care – particularly in Africa. Responsibility will also lie with funding bodies, such as the Cure Sickle Cell Disease Initiative of the US National Institutes of Health. Such work could serve as a model for developing therapies for other monogenic diseases. The time has come for an ambitious global genomic-research programme to uncover more genomic keys to sickle-cell disease therapy.

1. Esrick, E. B. et al. *N. Engl. J. Med.* **384**, 205–215 (2021).
2. Maitiro, S. N. et al. *PLoS ONE* **9**, e111464 (2014).
3. Manzel, S. et al. *Nature Genet.* **39**, 1197–1199 (2007).
4. Gurdasani, D., Barros, I., Zeggini, E. & Sandhu, M. S. *Nature Rev. Genet.* **20**, 520–535 (2019).
5. Walker, A. L. et al. *Blood* **118**, 5654–5670 (2011).



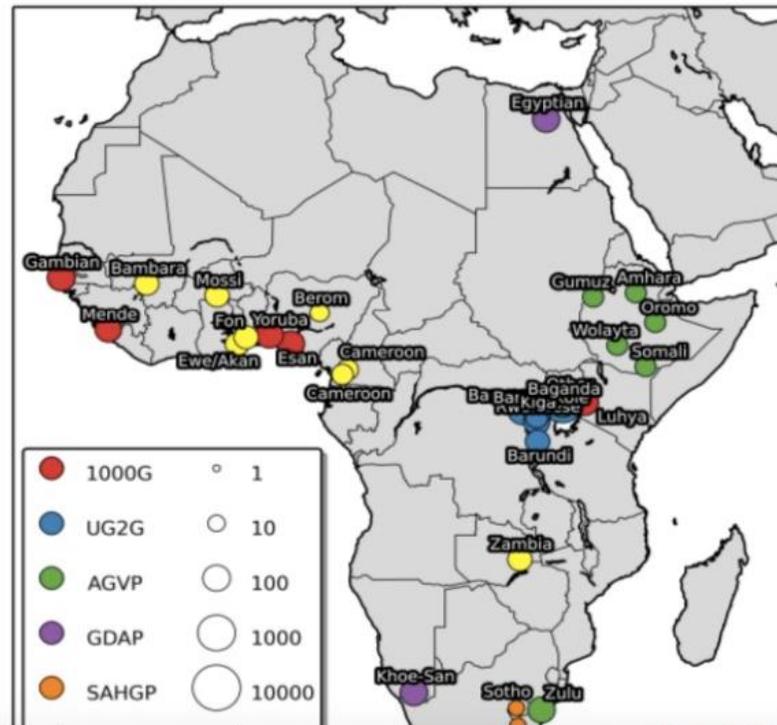
Wonkam, Br J Haematol. 2020 Dec;191(5):668-670
Ntatiro et al, PLoS One. 2014 Nov 5;9(11):e111464
Makani et al, Blood. 2011 Jan 27;117(4):1390-2
Wonkam et al, PLoS One. 2014 Mar 25;9(3):e92506.

H3Africa GWAS CHIP Design



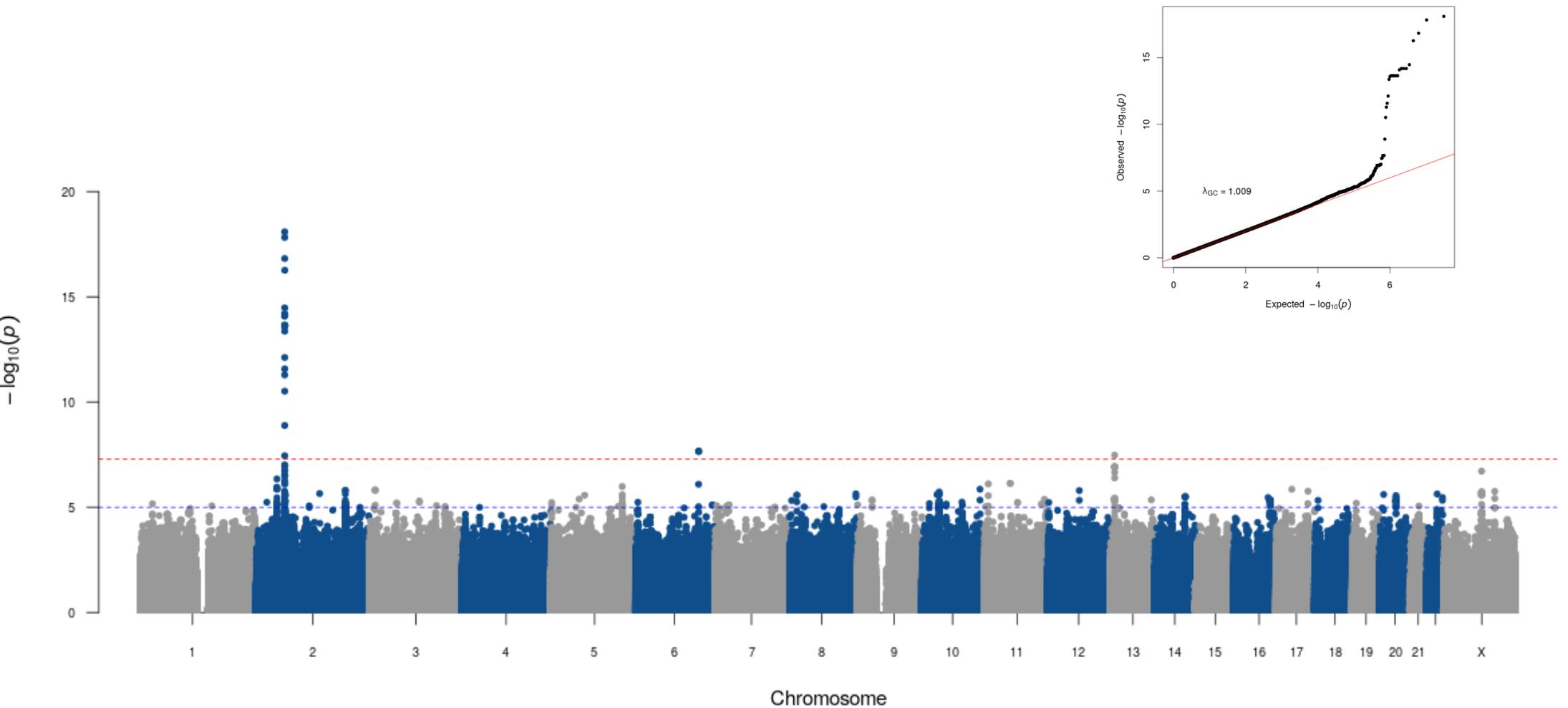
Sample size and distribution

| Source | Number of samples |
|------------|-------------------|
| GDAP | 204 |
| UG2G | 2000 |
| AGVP | 320 |
| 1000G | 507 |
| TrypanoGEN | 212 |
| Baylor | 348 |
| SAHGP | 16 |
| Total | 3607 |



2.5M SNPs, 700'000 selected from GWAS data from SSA

Novel HbF promoting loci in Africans



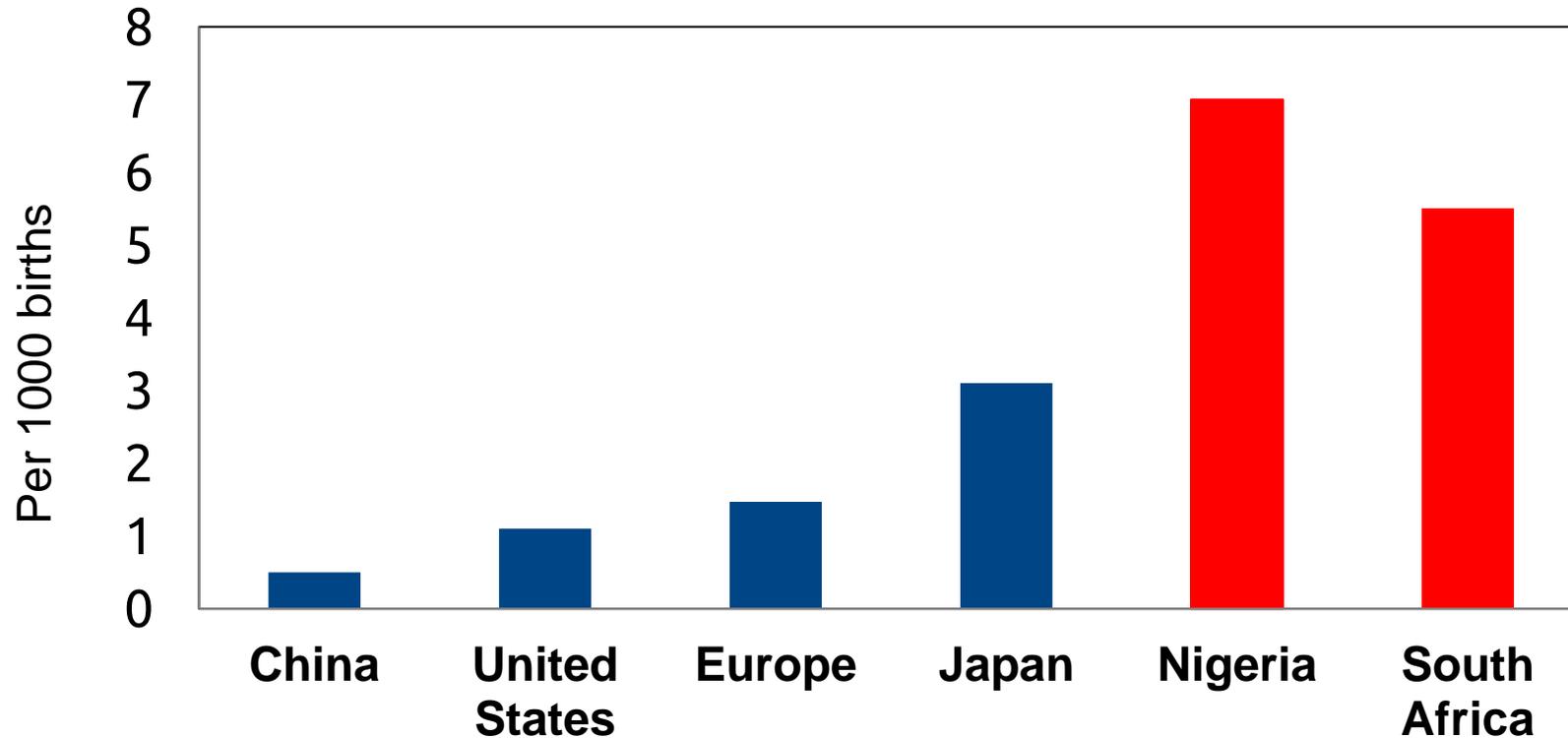
***Unknown in the Databases:
The case of a silent epidemic***

Global hearing health care: new findings and perspectives



Blake S Wilson, Debara L Tucci, Michael H Merson, Gerard M O'Donoghue

Number of Children Born with Hearing-loss



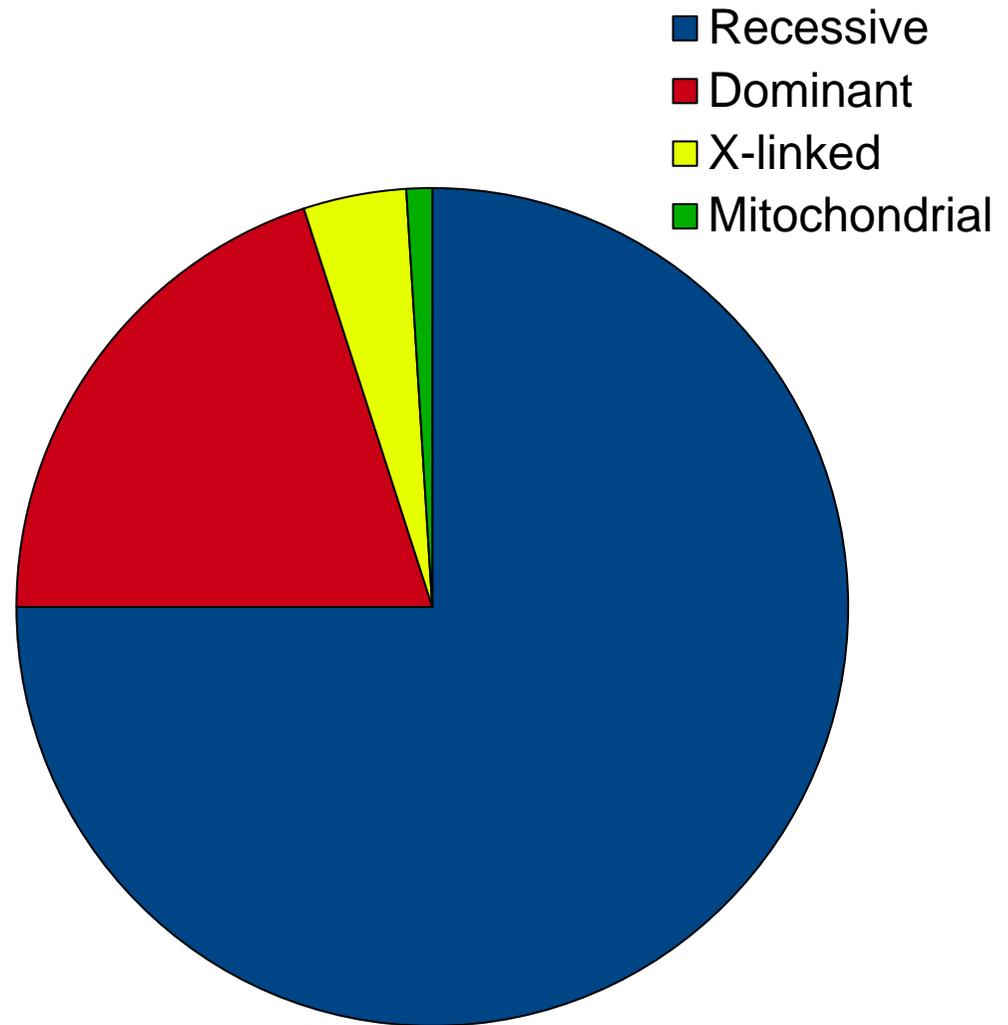
Congenital HI: 50 % Genetic

75% non-syndromic

> 90 non-syndromic loci

25% syndromic

> 400 syndromes



Syndromic Deafness

Waardenburg Syndrome Type II

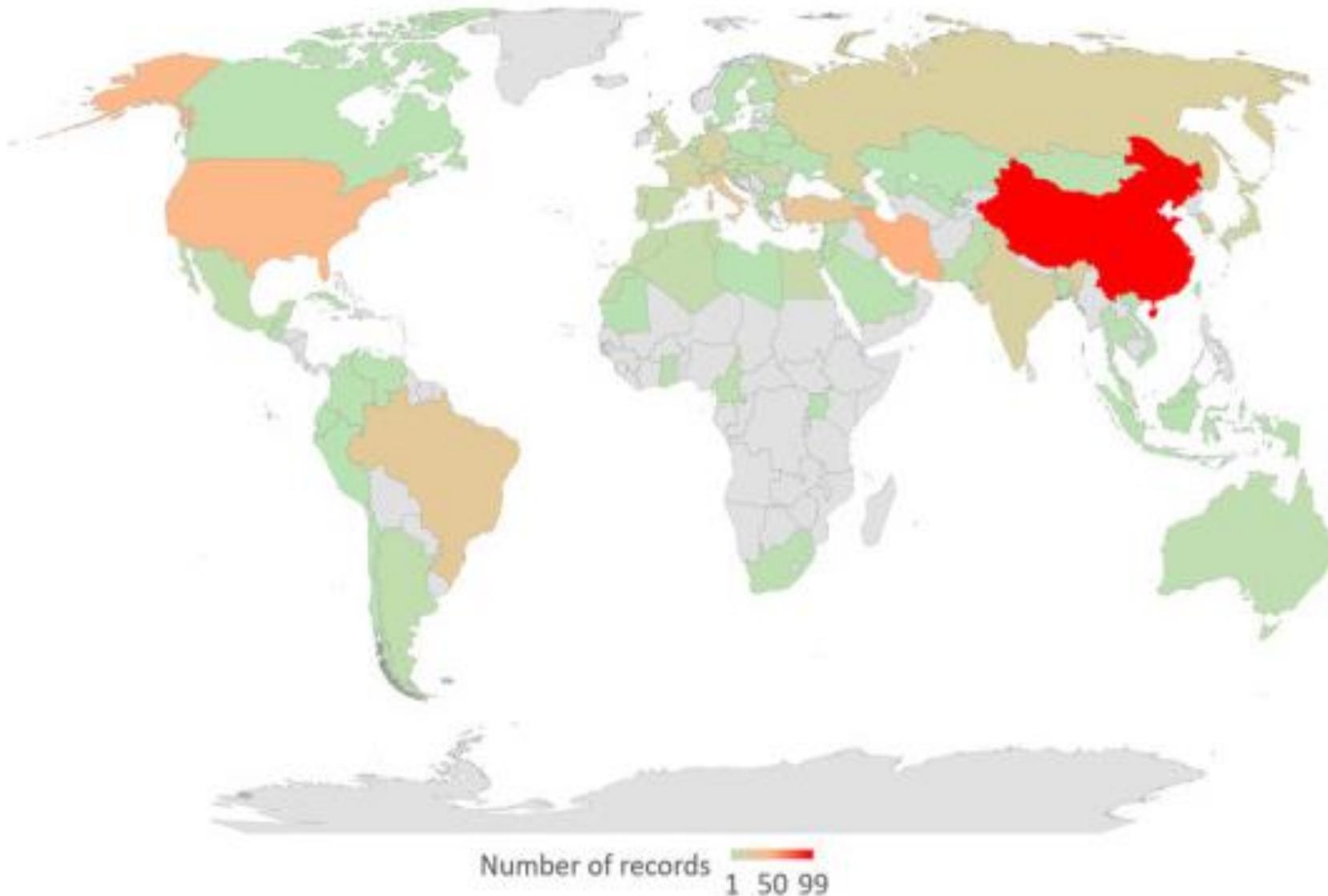
- 7% of genetic cases
- 50-60 % of syndromic cases



Wonkam et al., *Eur J Med Genet.* 2013;**56**:20-25.
Sellae & Beighton, *S Afr Med J.* 1983;63:725-728
Hageman MJ. *Trop Geog.* 1978;30(1):45-55.

Connexin Genes Variants Associated with Non-Syndromic Hearing Impairment: A Systematic Review of the Global Burden

Samuel Mawuli Adadey^{1,2,3}, Edmond Wonkam-Tingang³, Elvis Twumasi Aboagye^{2,3}, Daniel Wonder Nayo-Gyan⁴, Maame Boatemaa Ansong², Osbourne Quaye^{1,2}, Gordon A. Awandare^{1,2} and Ambroise Wonkam^{3,*}



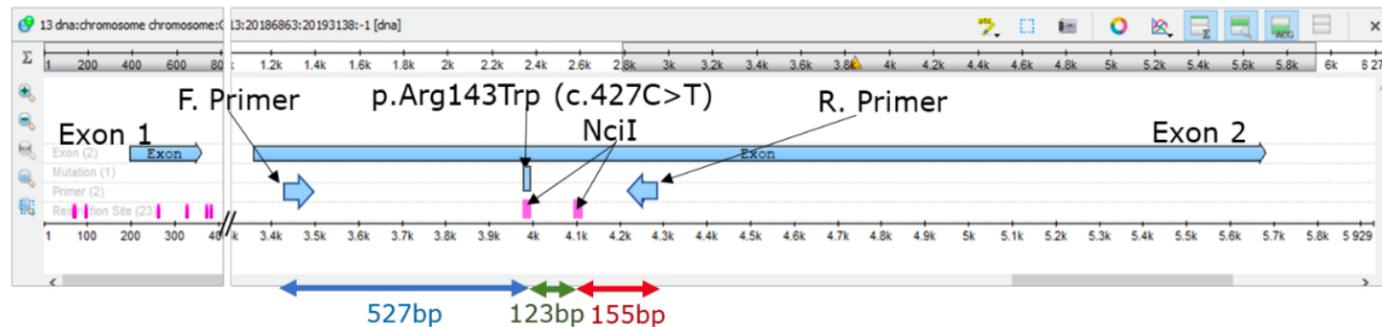
No PLP in *GJB2* in most Africans with NSHI

Article

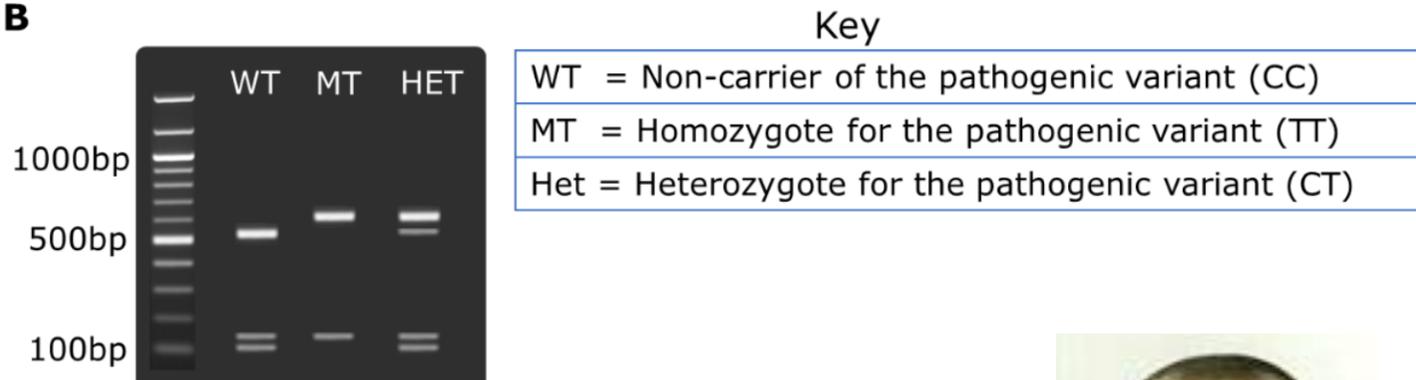
Enhancing Genetic Medicine: Rapid and Cost-Effective Molecular Diagnosis for a *GJB2* Founder Mutation for Hearing Impairment in Ghana

Samuel M. Adadey^{1,2} , Edmond Tingang Wonkam², Elvis Twumasi Aboagye¹, Darius Quansah¹, Adwoa Asante-Poku^{1,3}, Osbourne Quaye¹ , Geoffrey K. Amedofu⁴, Gordon A. Awandare¹ and Ambroise Wonkam^{2,*} 

A



B



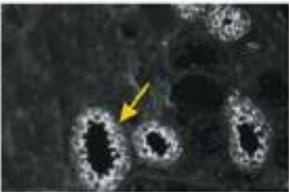
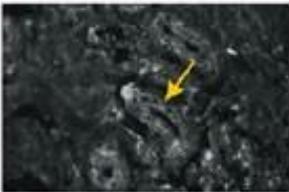
Article

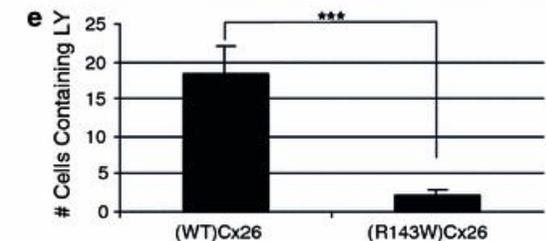
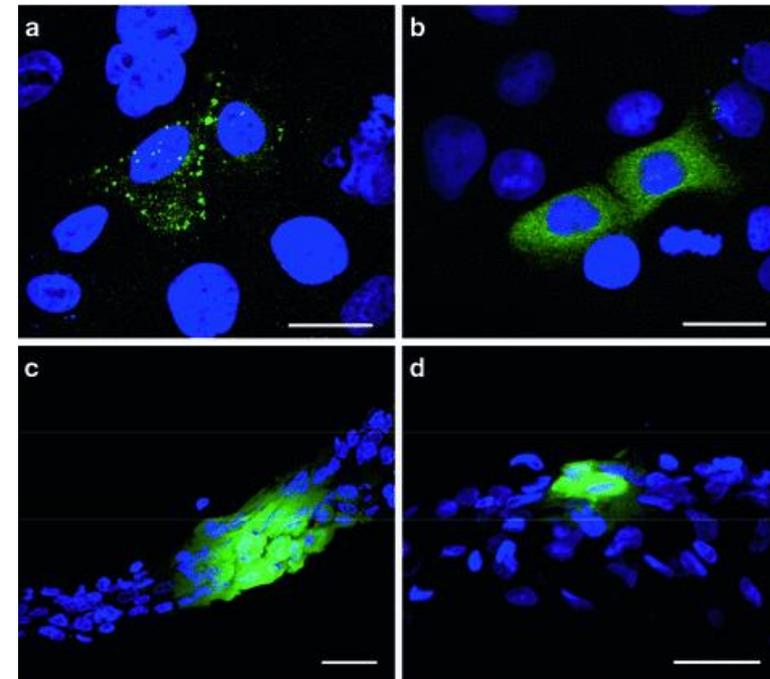
Age Estimate of *GJB2*-p.(Arg143Trp) Founder Variant in Hearing Impairment in Ghana, Suggests Multiple Independent Origins across Populations

Elvis Twumasi Aboagye^{1,2}, Samuel Mawuli Adadey^{1,2} , Kevin Esoh² , Mario Jonas², Carmen de Kock², Lucas Amenga-Etego¹, Gordon A. Awandare¹ and Ambroise Wonkam^{2,3,*} 



GJB2 Founder variant improve epithelial barrier *in vivo* and *in vitro*

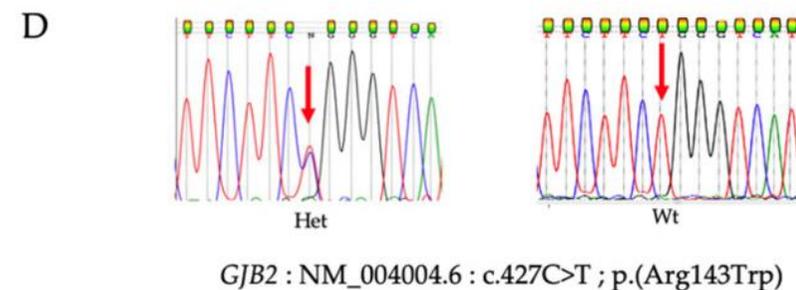
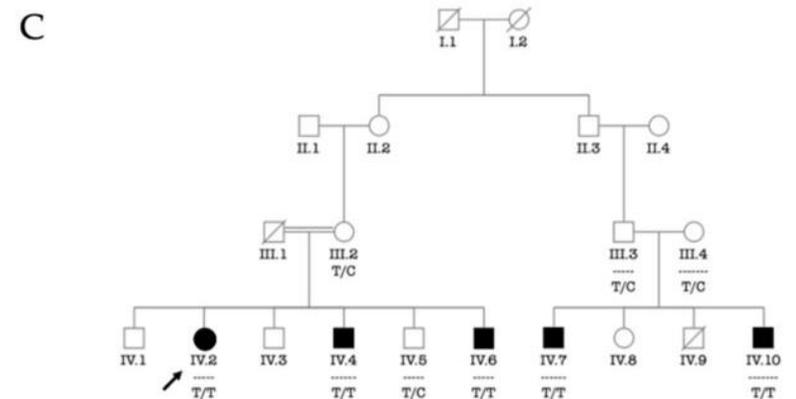
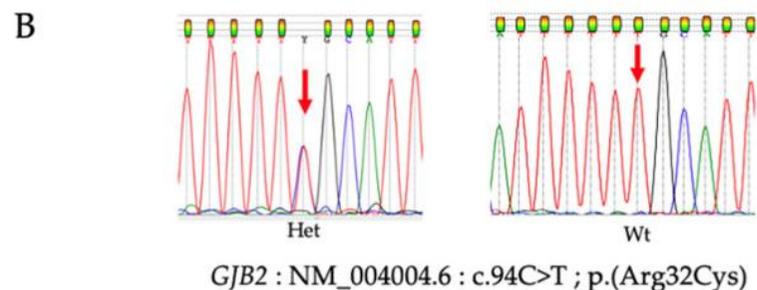
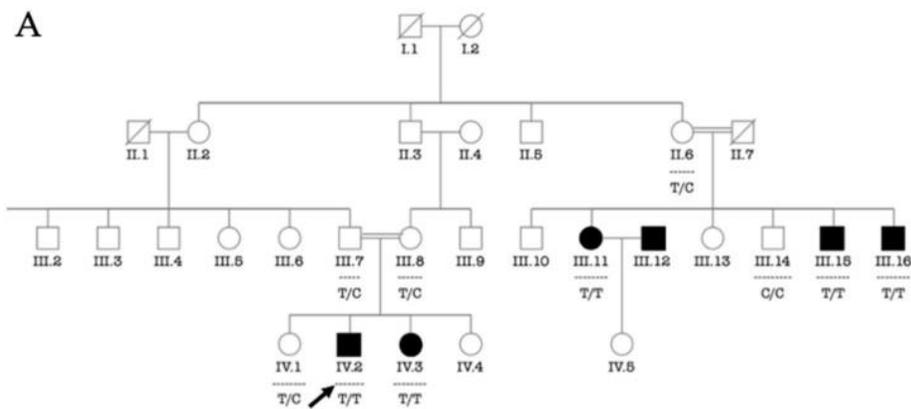
| GJB2 genotype | wt/wt | wt/R143W | R143W/R143W |
|---|--|--|--|
| Skin histology |  |  |  |
| Skin histometry | | | |
| Stratum corneum (μm) | 13.0 (10.7–14.0; n=5) | 14.7 (13.0–16.9; n=6) | 15.2 (11.9–17.1; n=7) |
| Epidermis (μm) | 44.7 (26.8–55.8; n=5) | 55.8 (46.7–60.1; n=6) | 59.0 (47.6–67.4; n=7) |
| Staining of eccrine sweat glands |  |  |  |
| Sweat analysis | | | |
| Sodium (mmol/L) | 22.7 (6.4–39.2; n=10) | 19.7 (10.2–36.2; n=11) | 60.1 (22.6–89.3; n=9) |
| Chloride (mmol/L) | 24.5 (6.0–43.0; n=10) | 20.0 (8.0–44.0; n=11) | 55.0 (10.0–70.0; n=9) |



NATURE MEDICINE; 8: 12 : 1332-3 (2002)

GJB2 Is a Major Cause of Non-Syndromic Hearing Impairment in Senegal

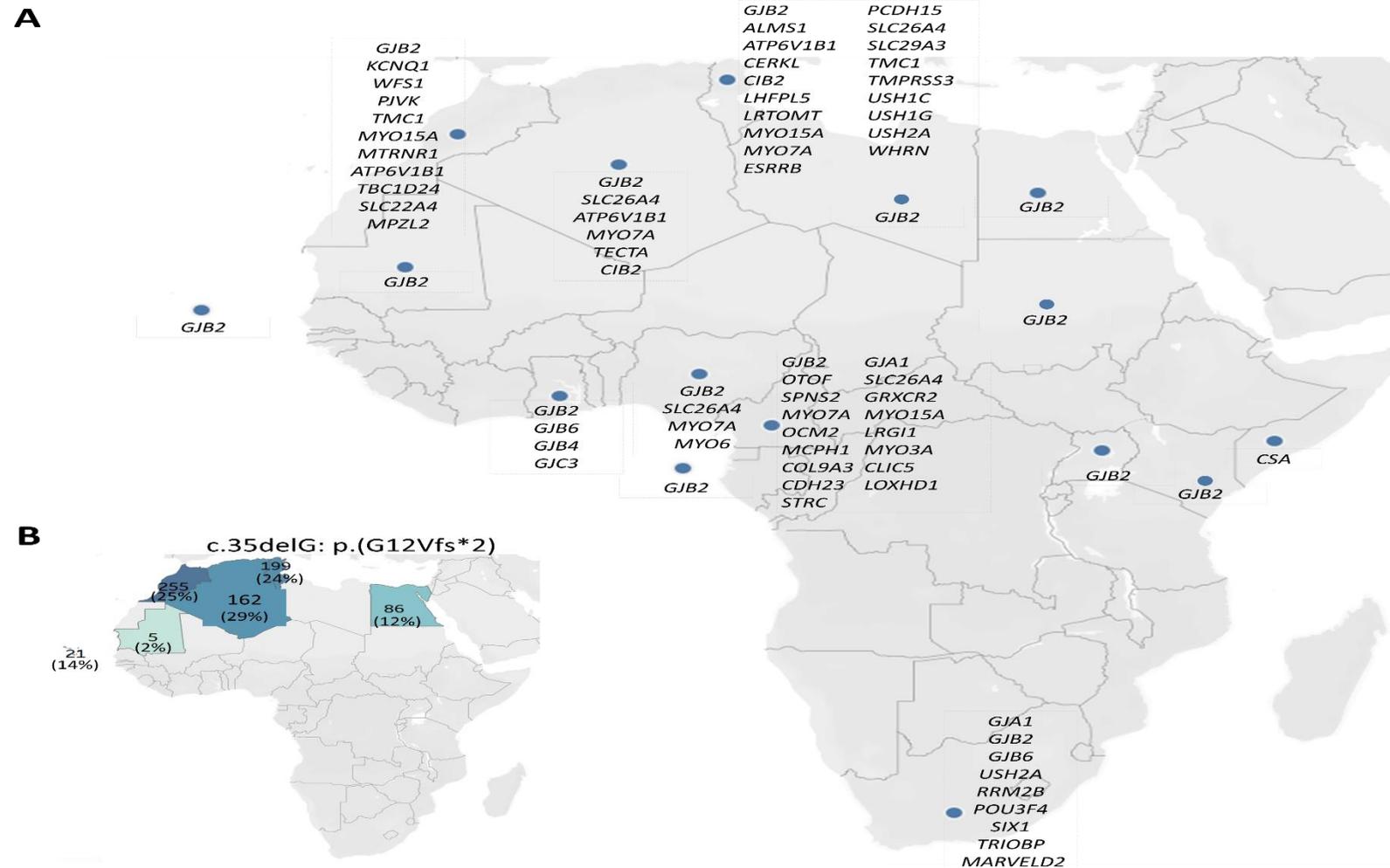
Yacouba Dia¹, Samuel Mawuli Adadey^{2,3} , Jean Pascal Demba Diop¹, Elvis Twumasi Aboagye², Seydi Abdoul Ba¹, Carmen De Kock², Cheikh Ahmed Tidjane Ly¹, Oluwafemi Gabriel Oluwale², Andrea Regina Gnilane Sène¹, Pierre Diaga Sarr¹, Bay Karim Diallo⁴, Rokhaya Ndiaye Diallo¹ and Ambroise Wonkam^{2,5,*} 



Americas ← →



A few Hearing Impairment Studies from Africa



Human Genetics
<https://doi.org/10.1007/s00439-021-02376-y>

REVIEW



Hearing loss in Africa: current genetic profile

Samuel Mawuli Adadey^{1,2} · Edmond Wonkam-Tingang² · Elvis Twumasi Aboagye¹ · Osbourne Quaye¹ · Gordon A. Awandare¹ · Ambrose Wonkam²

Rare and Novel HI Genes in Africa

A novel variant in *DXML2* gene is associated with autosomal dominant non-syndromic hearing impairment (DFNA71) in a Cameroonian family

Edmond Wonkam-Tingang¹, Isabelle Schrauwen², Kevin K Esoh¹ , Thashi Bharadwa Liz M Nouel-Saied² , Anushree Acharya², Abdul Nasir³ , Suzanne M Leal² and Ambroise Wonkam¹ 

Bi-Allelic Novel Variants in *CLIC5* Identified in Cameroonian Multiplex Family with Non-Synd Hearing Impairment

Edmond Wonkam-Tingang¹, Isabelle Schrauwen² , Kevin K. Esoh¹ , Thashi Bharadwa Liz M. Nouel-Saied² , Anushree Acharya², Abdul Nasir³ , Samuel M. Adadey^{1,4} , Shaheen Mowla⁵ , Suzanne M. Leal² and Ambroise Wonkam^{1,*} 

Whole exome sequencing reveals a biallelic frameshift mutation in *GRXCR2* in hearing impairment in Cameroon

Ambroise Wonkam^{1,2}  | Kamogelo Lebeko¹ | Shaheen Mowla³ | Jean Jacques N Mike Chong⁵ | Guillaume Pare⁵

Whole exome sequencing identifies rare coding variant human-mouse ortholog genes in African individuals with non-syndromic hearing impairment

Oluwafemi G Oluwola¹ , Kevin K Esoh¹ , Edmond Wonkam-Tingang¹, *Experimental Biology and Medicine* 2021; **246**: 197–206  and Ambroise Wonkam¹ 
Mol Genet Genomic Med. 2021;00:e1609.

Genes 2020, 11, 1249; doi:10.3390/genes11111249

Experimental Biology and Medicine 2021; 0: 1–9. |

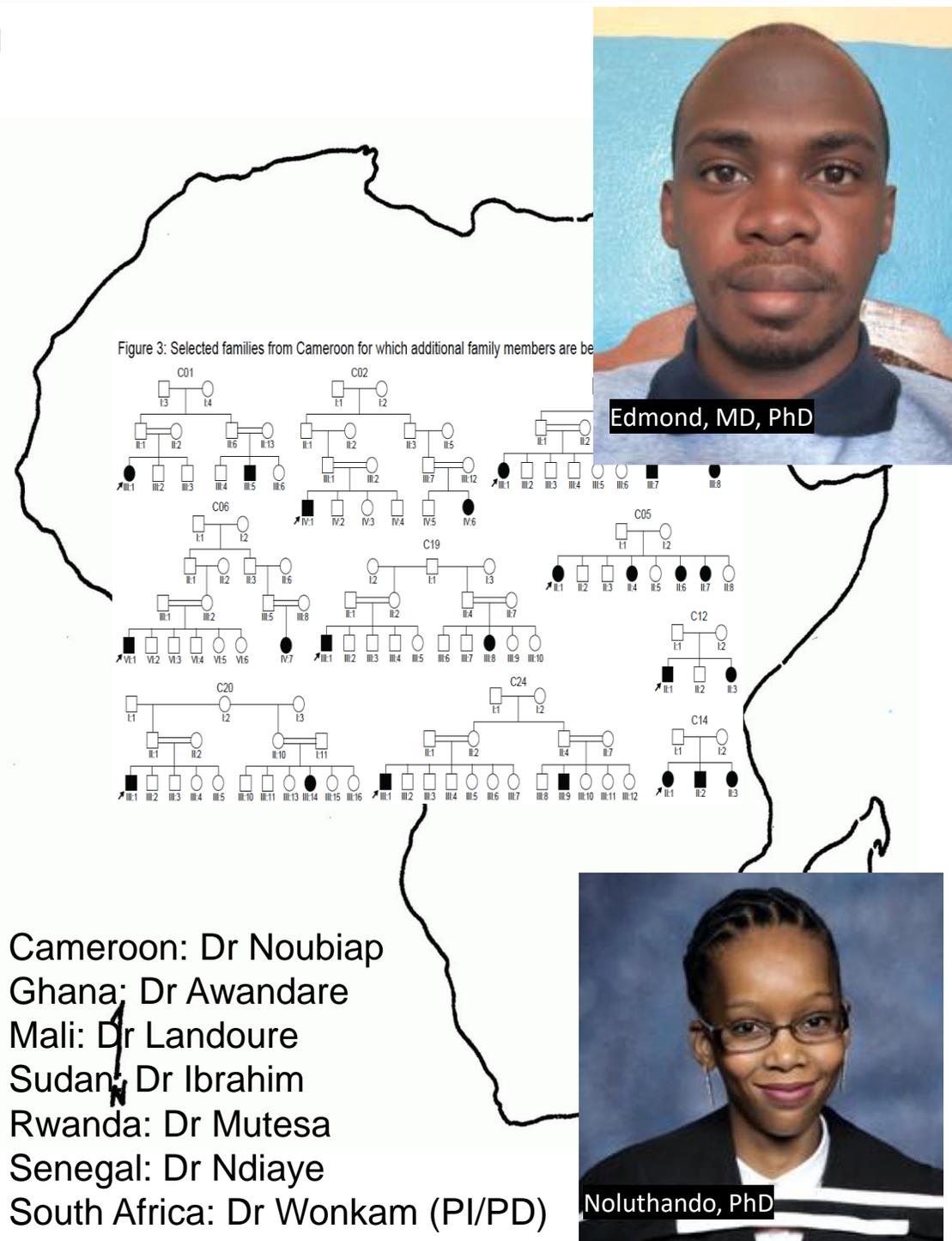


Figure 3: Selected families from Cameroon for which additional family members are being recruited. The figure shows a map of Africa with several family trees overlaid on different regions. The families are labeled C01, C02, C05, C06, C12, C14, C19, C20, and C24. Each tree shows multiple generations of individuals, with some individuals marked with a black square indicating hearing impairment. A portrait of Edmond, MD, PhD is in the top right, and a portrait of Noluthando, PhD is in the bottom right.

Cameroon: Dr Noubiap
Ghana: Dr Awandare
Mali: Dr Landoure
Sudan: Dr Ibrahim
Rwanda: Dr Mutesa
Senegal: Dr Ndiaye
South Africa: Dr Wonkam (PI/PD)

<https://doi.org/10.1038/s42003-022-03326-8>

OPEN

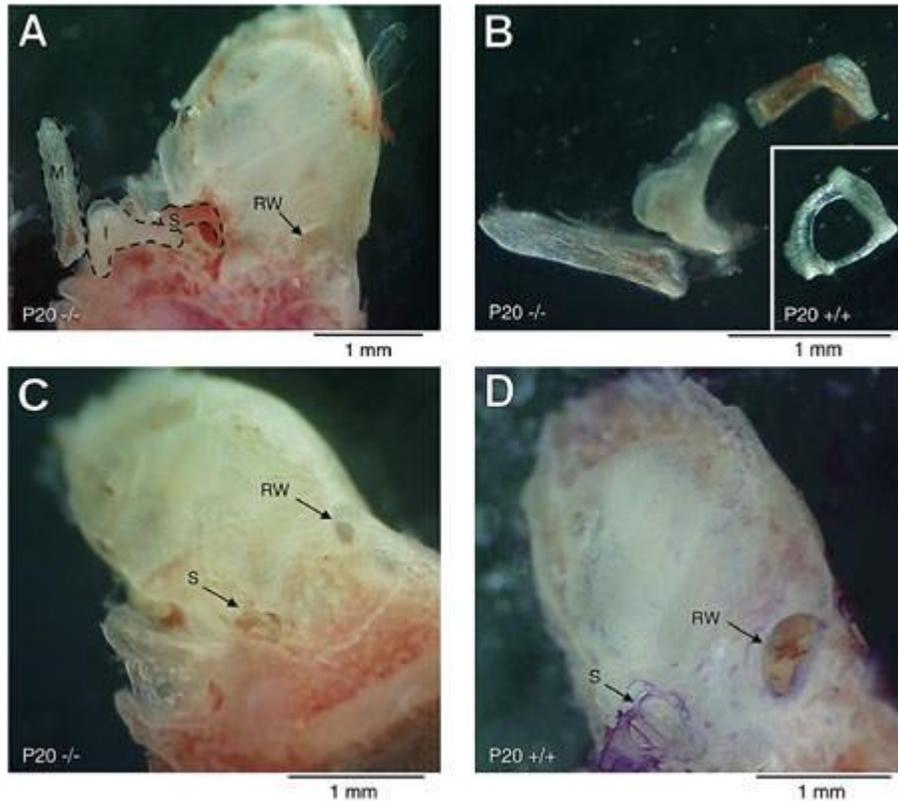
Exome sequencing of families from Ghana reveals known and candidate hearing impairment genes

Ambroise Wonkam ^{1,2,8} ⁸, Samuel Mawuli Adadey ^{1,3,8}, Isabelle Schrauwen⁴, Elvis Twumasi Aboagye³, Edmond Wonkam-Tingang¹, Kevin Esoh ¹, Kalinka Popel¹, Noluthando Manyisa¹, Mario Jonas¹, Carmen deKock¹, Victoria Nembaware¹, Diana M. Comejo Sanchez⁴, Thashi Bharadwaj⁴, Abdul Nasir ⁵, Jenna L. Everard ⁴, Magda K. Kadlubowska⁴, Liz M. Nouel-Saied⁴, Anushree Acharya⁴, Osbourne Quaye ³, Geoffrey K. Amedofu⁶, Gordon A. Awandare ³ & Suzanne M. Leal^{4,7} ⁷

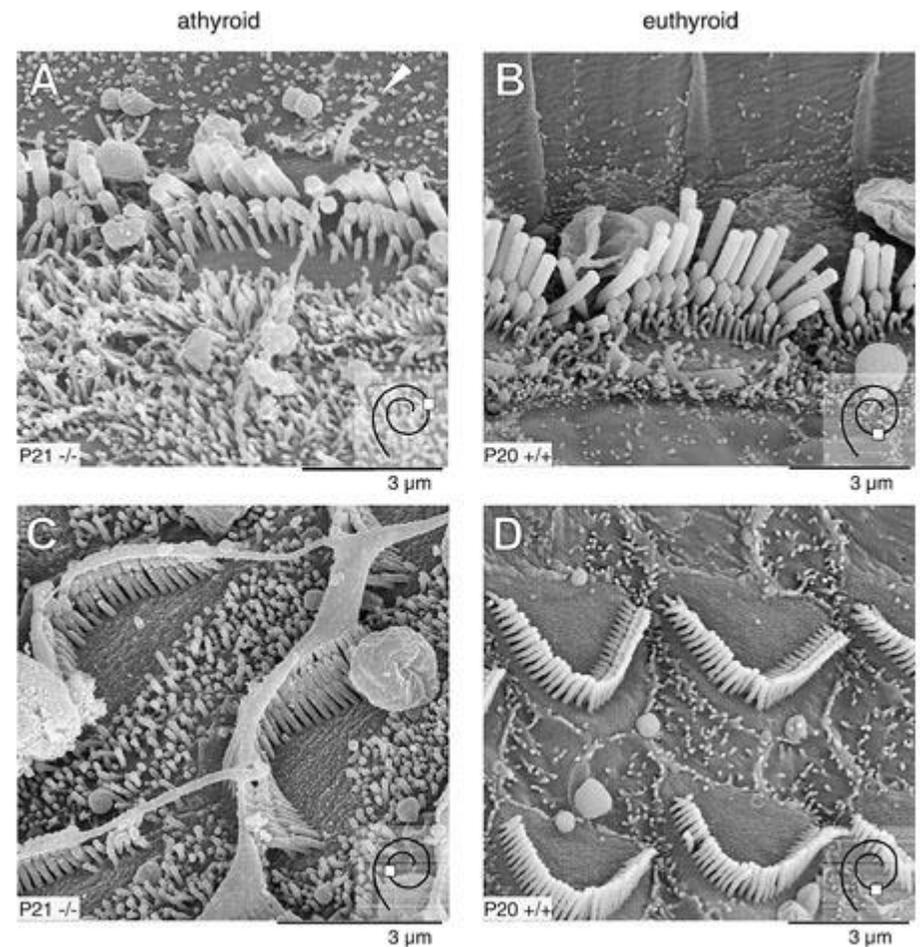


Waardenburg Syndrome: Novel *PAX8* Gene

Pax 8 ^{-/-} Mice



Inner Ear of Athyroid Mice Is Immature



The micrograph along the cochlear partition

Generating Assets, Knowledge & Solutions



H3Africa
Human Heredity & Health in Africa

Home

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- Datasets: 20
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Policy documents

H3Africa

The Human Heredity and Health in Africa (H3Africa) is a contemporary research approach to the study of genetic determinants of common diseases with the goal of improving health outcomes in African populations. Data and biospecimens from H3Africa projects, with access controlled by a Data and Biospecimen Access Policy, are housed in the European Genome-phenome Archive and three H3Africa biorepositories.

This catalogue enables users to search for datasets or biospecimens. Users can browse the catalogue using the simple search or the advanced search. For more advanced searching or to request access to data, please contact the H3Africa Data and Biospecimen Access Committee.

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| Available Studies | | | | | | | |
|--|------------|--------------|---------------------------------|--|--------------|--------------|--------|
| Title | Acronym | Design | EGA Accession | Data use codes | Participants | Biospecimens | Paired |
| The Genomics of Schizophrenia in the South African Xhosa People | SAX | | Unavailable | Unavailable | 0 | 2238 | 0 |
| Genetic determinants of susceptibility to trypanosomiasis | TrypanoGEN | Case | EGAS00001002602 | DUO:0000006 DUO:0000027 DUO:0000024 DUO:0000019 DUO:0000021 | 233 | 0 | 0 |
| H3Africa Chip Design Study | H3AChip | Control | EGAS00001002976 | DUO:0000006 DUO:0000027 DUO:0000024 DUO:0000019 DUO:0000021 | 348 | 379 | 104 |
| Stroke Investigative Research & Educational Network | SIREN | | Unavailable | Unavailable | 0 | 6001 | 0 |
| Collaborative African Genomics Network | CAFGEN | Case-Control | EGAS00001002656 | DUO:0000006 DUO:0000027 DUO:0000024 DUO:0000019 DUO:0000021 | 314 | 1804 | 306 |
| Genomic and Environmental Risk Factors for Cardiometabolic Disease in Africans | AWI-Gen | Case-Control | EGAS00001002482 | DUO:0000006 DUO:0000027 DUO:0000024 DUO:0000019 DUO:0000014 DUO:0000015 | 971 | 13415 | 0 |



Bongani Mayosi: 'Lift as you rise ...'



Clair, MSc.



Amber, MSc.



Robyn, MSc.



Amy, MSc., PhD



Nomlindo, MBChB



Cedrik, MD, MMed



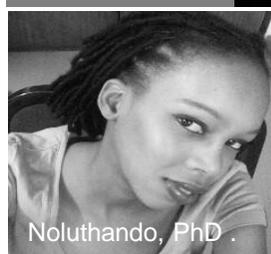
Khuthala, PhD.



Tshepiso, MSc.



Kathryn, MSc



Noluthando, PhD



Jean-Jacques, MD, PhD



Valentina, PhD, UY1



Chantelle, MSc.



Samuel, PhD, UG



Kamogelo, PhD



Gift Dineo, PhD



Jason, PhD



Maryam, MSc.



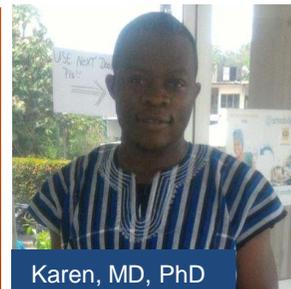
Elvis, PhD



Edmond, MD, PhD



Abdoulaye, MD, PhD



Karen, MD, PhD

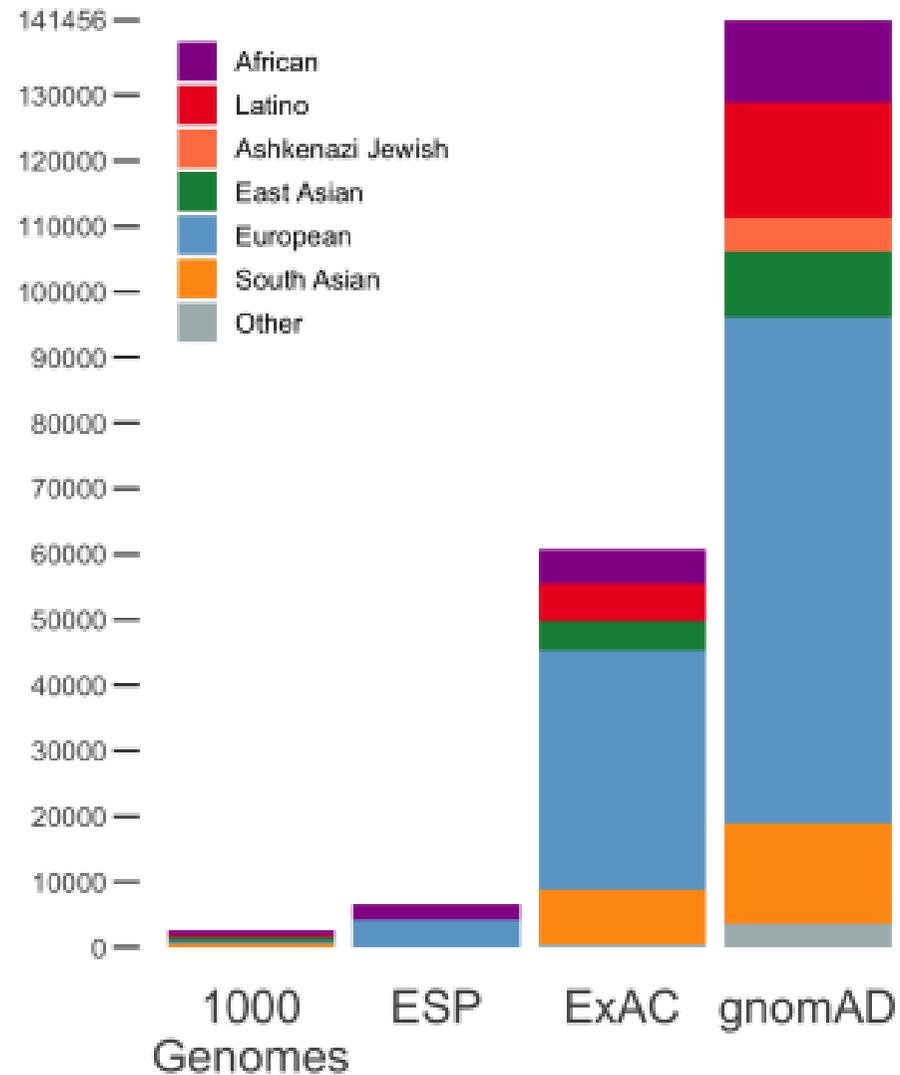


Ayman, MD, MMed



Malick, MD, PhD

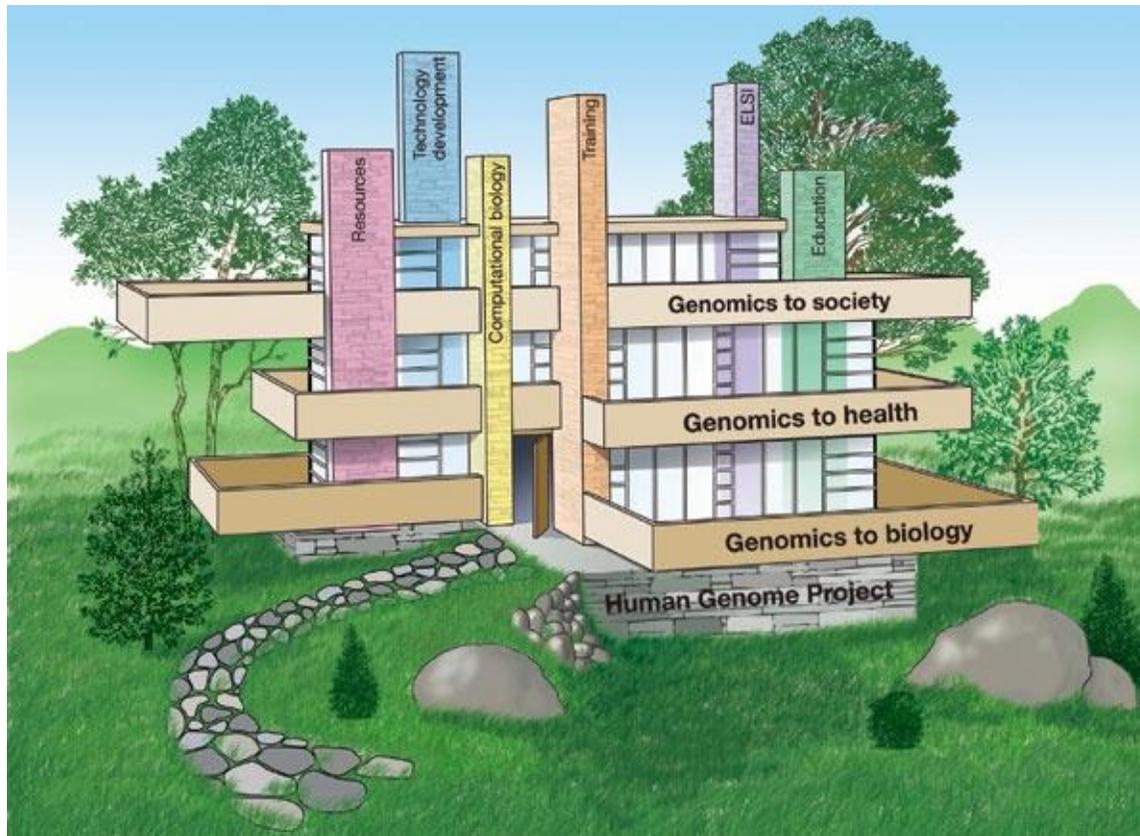
Addressing the Exome DB Diversity



Nature. 2016 August 18; 536(7616): 285–291.

The road ahead in genetics and genomics

Amy L. McGuire, Stacey Gabriel, Sarah A. Tishkoff , Ambroise Wonkam ,



NATURE REVIEWS | GENETICS

African ancestry and ecosystems motivate investments in African genomic variations, as a scientific imperative, with equitable access being a challenge to be addressed, to fully meet the potential of the next frontier of global genetic medicine.

Sequence three million genomes across Africa

Ambroise Wonkam

Middle East & Africa

The Economist June 26th 2021 47



Science

The African genome project

CAPE TOWN

A Cameroonian professor plans to fill a gaping hole in humanity's understanding of its own genetics

WHEN THE Mutambaras' first son was about 18 months old they began to worry about his hearing. The toddler did not respond when asked to "come to Mama". He was soon diagnosed as deaf,

around 1m genomes as part of an effort to refine the "reference genome", a blueprint used by researchers. But less than 2% of all sequenced genomes are African, though Africans are 17% of the world's population

Africa. Unfortunately, that diversity is also reflected in the greater variety of genetic illnesses found there.

The bias in sequencing leads to underdiagnosis of diseases in people of (relatively recent) African descent. Genetic causes of heart failure, such as the one that caused the ultimately fatal collapse of Marc-Vivien Foé, a Cameroonian football player, during a game in 2003, are poorly understood. The variation present in most non-Africans with cystic fibrosis is responsible for only about 30% of cases in people of African origin. This is one reason, along with its relative rarity, that the illness is often

cover ethnolinguistic, regional and other groups. Therefore, we aim to start such a project, called the Three Million African Genomes (3MAG), which would build capacity on the continent – in genomics research and its applications, and governance. The findings would bring benefits worldwide, including some that are hard to anticipate. In a similar way, much knowledge put to use during the COVID-19 pandemic – from public commu-

LE TEMPS SAMEDI 9 OCTOBRE 2021

4 International

La génétique africaine au service de l'humanité

RECHERCHE Professeur à l'Université du Cap, le Camerounais Ambroise Wonkam était l'invité du Geneva Science and Diplomacy Anticipator. Le généticien veut réaliser le profil ADN de 3 millions d'Africains. Une manière de combler une lacune: le séquençage génomique de 2003 est très «eurocentrique»

STEPHANE BISSARD
@StephaneBissard

Quand il nous parle de l'ascension d'un 4000 mètres à Saas-Fee, des blesses le long desquels il s'est souvent baladé ou quand il évoque ces moments d'unité chaleureuse devant un emballage, difficile de ne pas y voir un once de nostalgie. Ambroise Wonkam aime le White. Il y a travaillé l'hôpital de Stion et y a encore de nombreux amis. C'est Camerounais de 31 ans, enjoué, qui a grandi dans la ville de la fournaise, vit au jour le jour à Cap, en Afrique du Sud. C'est l'un des généticiens africains les plus pointus du moment.

Tratamiento de malades

tion. Professeur au sein de la Division génétique de la faculté des sciences médicales à l'Université du Cap, il veut combler une lacune majeure: le séquençage du génome, en 2003, a été une avancée extraordinaire. Sauf que les données génétiques ainsi obtenues ne contiennent que 2% des gènes africains. Motif: la recherche a surtout été financée en Europe et en Amérique du Nord. De plus, selon la limite de généticiens en Afrique a aussi joué un rôle.

«On oublie l'origine de l'humanité, dit-il. La génétique. Trois millions de variantes ne sont pas présentes dans la base de données du génome. 10% des données relatives au génome sont issues de la population européenne. C'est

devenu soutien financier rare, mais précieux des National Institutes of Health (NIH) aux États-Unis et du Wellcome Trust en Grande-Bretagne. Le projet 3MAG a un coût évalué à 450 millions de dollars par an sur dix ans. «C'est un véritable défi de l'humanité», relève le chercheur qui se dit «fier, en tant qu'Africain, de pousser les frontières de la génétique un peu plus loin».

Le séquençage de génomes africains aurait des bénéfices à terme non seulement pour l'Afrique, mais pour le planète entière. Comme le rappelle Ambroise Wonkam, sur les 3000 gènes que possède l'être humain, 25% d'entre eux sont associés à une maladie. Comprendre les



PORTRAIT

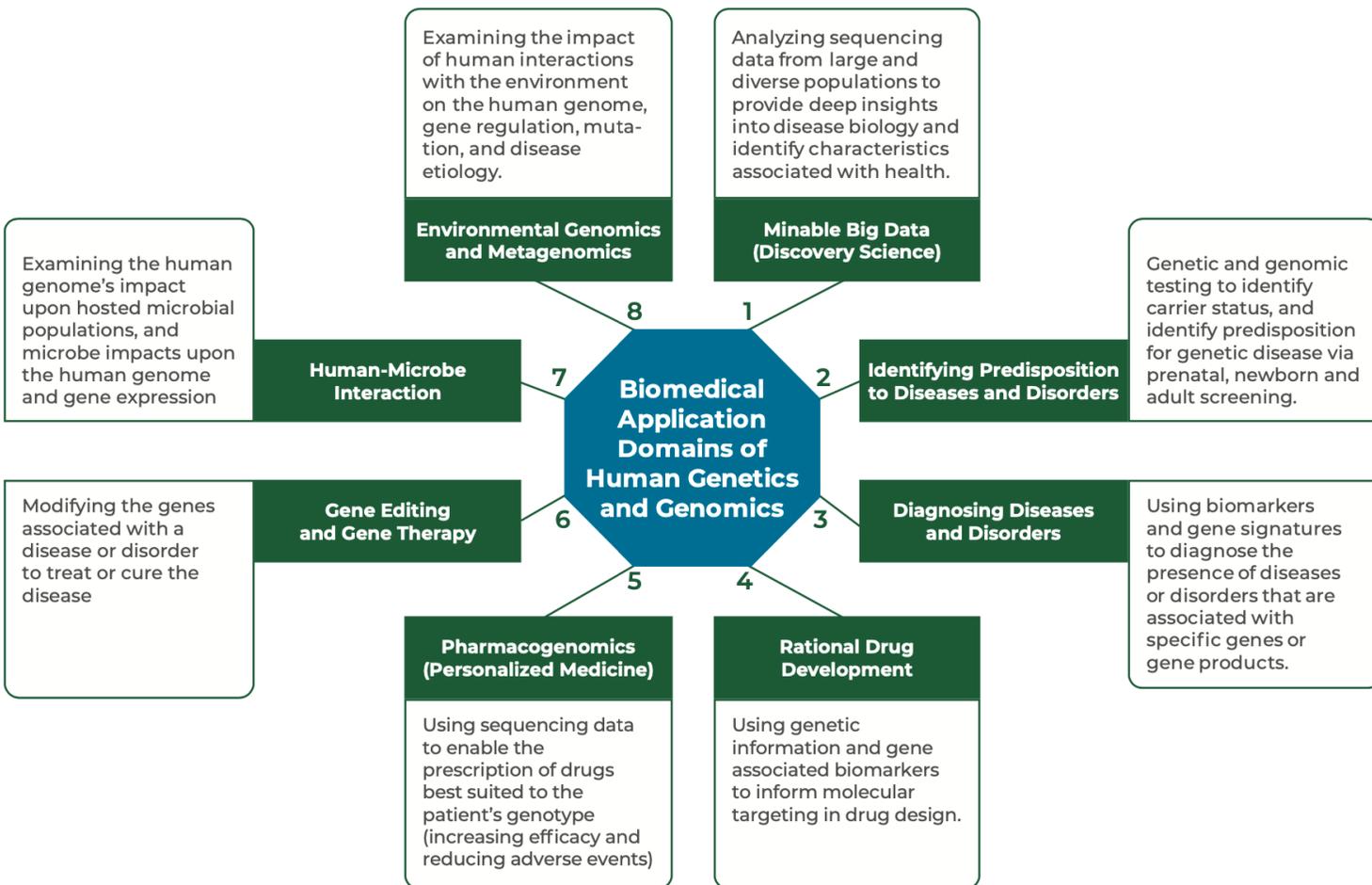
The Economic Impact and Functional Applications of Human Genetics and Genomics

Commissioned by the American Society of Human Genetics

Produced by TEconomy Partners, LLC.

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May 2021



\$3.3B
FEDERAL RESEARCH



152,000
INDUSTRY JOBS



850,000
TOTAL SUPPORTED JOBS



\$265B
TOTAL ECONOMIC IMPACT



\$5.2B
DIRECT FEDERAL TAX REVENUES



4.75:1.00
FEDERAL RETURN ON INVESTMENT

ASANTE SANA/ENKOSI/THANKS!



HI GeneSAfrica
Hearing Impairment Genetics Studies in Africa

NIH: 1.25 million USD (PD/PI)
AESA/Wellcome trust: 2.07million USD

1 U01 HG009716-01

Ref: H3A/18/001



IFGeneRA
Individual Findings in Genomics
Research in Africa

NIH: 2.6 million USD (PD/PI)

1U54HG009790-01



Wellcome Trust- DELTAS (Co-I)
1/5 million USD (Parent grant: 7.2 million USD)

Ref: 107755Z/15/Z



NIH 4.3 million USD (PD/PI)

1 U24 HL135600-01

1 U01 HG007459-01

