Frontiers in Population Genomics: Research Directions for NHGRI

Health and Health Disparities of US Race/Ethnic Minority Populations

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Need for large population studies in multiple ethnic groups

- Opportunity to design studies
  - that are not unduly influenced by black/white comparison
  - study and understand non-traditional risk factors – e.g., psychosocial stressors
  - adequately powered GxE analyses modeling group (e.g., ethnicity) influence
  - take advantage of ongoing understanding of biology - Epigenetics – methylation (cancers, diabetes, infant mortality)
  - Continue to update our understanding and measurement of observable traits.
- Opportunity to incorporate new thinking – e.g., relationship between

  gut flora and human diseases
  - inflammatory bowel disease, colon cancer
  - homeostasis of the immune system

  Intra-uterine environment - diabetes

Need for large population studies in multiple ethnic groups

Sciencexpress Report

Replication of Genome-Wide Association Signals in U.K. Samples Reveals Risk Loci for Type 2 Diabetes

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Sciencexpress Report

Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels

Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes for BioMedical Research*†

Sciencexpress Report

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen L. Mohlke,[2] Lori L. Bonnycastle,[3] Cristen J. Willer,[1] Yun Li,[1] William L. Duren,[1] Michael R. Erdos,[3] Heather M. Stringham,[1] Peter S. Chines,[3] Anne U. Jackson,[1] Ludmila Prokunina-Olsson,[3] Chia-Jen Ding,[1] Amy J. Swift,[3] Narisu Narisu,[3] Tianle Hu,[1] Randall Pruim,[4] Rui Xiao,[1] Xiao-Yi Li,[1] Karen N. Conneely,[1] Nancy L. Riebow,[3] Andrew G. Sprau,[3] Maurine Tong,[3] Peggy P. White,[3] Kurt N. Hetrick,[3] Michael W. Barnhart,[3] Craig W. Bark,[3] Janet L. Goldstein,[3] Lee Watkins,[3] Fang Xiang,[1] Jouko Saramies,[6] Thomas A. Buchanan,[7] Richard M. Watanabe,[8,9] Timo T. Valle,[10] Leena Kinnunen,[10,11] Gonçalo R. Abecasis,[1] Elizabeth W. Pugh,[3] Kimberly F. Doheny,[3] Richard N. Bergman,[9] Jaakko Tuomilehto,[10,11,12] Francis S. Collins,[3]* Michael Boehnke[1]*

Expanding our understanding of Human Genetic Variation

A second generation human haplotype map of over 3.1 million SNPs

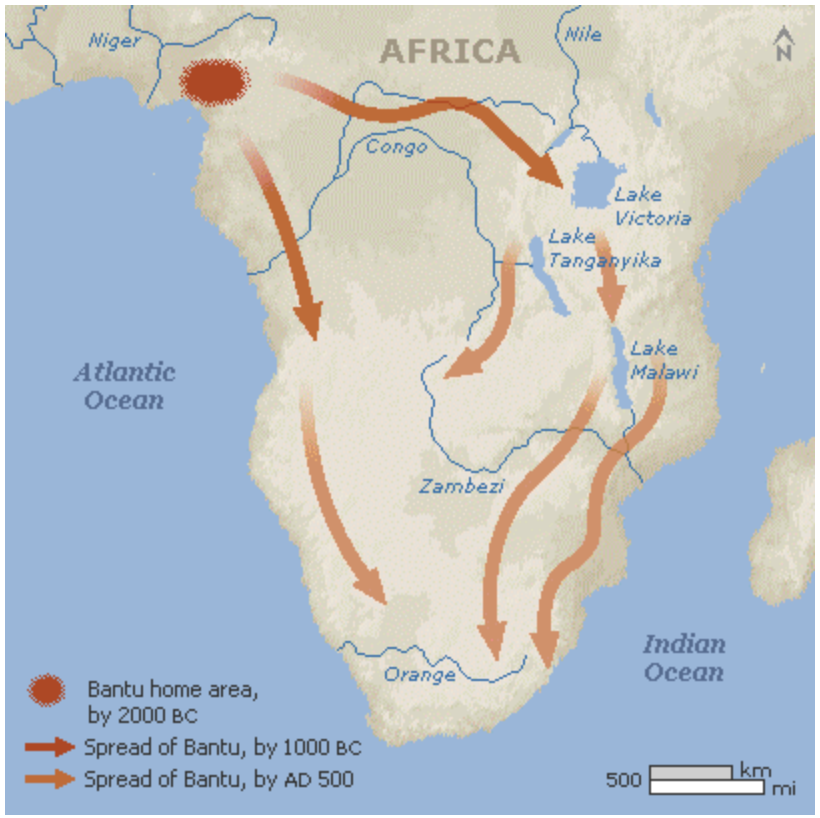
Table 3 | Number of tag SNPs required to capture common (MAF ≥ 0.05) Phase II SNPs

Threshold	YRI	CEU	CHB+JPT
$r^2 \geq 0.5$	627,458	290,969	277,831
$r^2 \geq 0.8$	1,093,422	552,853	520,111
$r^2 = 1$	1,616,739	1,024,665	1,078,959

Sampling Africa Suggestion

1. Need to engage African scientists to systematically sample Africa
2. Engaging African professional organizations interested in genomics in Africa will be helpful (e.g., African Society of Human Genetics).
3. Sampling should be based on clear understanding of both ancient and recent migrations within and out-of-Africa (e.g., Bantu expansion)

Bantu Migration



San man from Namibia

1000 – 2000 years old San-paintings near Murewa (Zimbabwe)

1) **Second-largest of the seven continents on Earth**
2) **Covers 11,700,000 square miles.**
3) **53 countries in Africa.**
4) **Pre-history - No nation state - inhabited by groups of hunter-gatherers (e.g.,the Khoi & San)**
5) **936 million people (~ 13% of the world's population in Africa).**
6) **African people are remarkably diverse**
7) **Speak a vast number of different languages**
8) **Practice hundreds of distinct religions**
9) **Live in a variety of types of dwellings & Engage in a wide range of economic activities.**

A genome-wide association study identifies alleles in *FGFR2* associated with risk of sporadic postmenopausal breast cancer

# of SNPs tagged using the pairwise method at r^2 of 0.8 at various minor allele frequencies

	Population	Minor allele frequency (MAF) cut-off				
		0.001	*0.01*	*0.03*	*0.05*	*0.10*
FGFR2	**YRI**	105	101	93	84	66
	CEU	53	43	39	34	23
TNRC9	**YRI**	45	44	40	36	30
	CEU	21	18	17	16	15

Note that the tag SNP sets largely overlap and the CEU set is mostly a subset of the YRI one

Interpretation of Biomedical (genetics) Results

Workshop to guide (increase sensitivity) interpretation of results.

Genome-wide detection and characterization of positive selection in human populations

Pardis C. Sabeti[1*], Patrick Varilly[1*], Ben Fry[1], Jason Lohmueller[1], Elizabeth Hostetter[1], Chris Cotsapas[1,2], Xiaohui Xie[1], Elizabeth H. Byrne[1], Steven A. McCarroll[1,2], Rachelle Gaudet[3], Stephen F. Schaffner[1], Eric S. Lander[1,4,5,6] & The International HapMap Consortium†

Nature **449**, 913-918 (18 October 2007)

Population	Gene	Selection Pressure
Ibadan, Nigeria	LARGE, DMD	Infection – Lassa virus
Utah, USA	SCL24A5, SLC45A2	Skin Pigmentation in Europe
China/Japan	EDAR & EDA2R	Development of hair follicles in Asia

These and other published data show clearly that there are regional variations in the evolutionary forces that shaped the human genome.

Genome-wide detection and characterization of positive selection in human populations

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Interpretation – "In the African samples (Yoruba in Ibadan, Nigeria), there is evidence of selection for two genes with well-documented biological links to the Lassa fever virus."

Richmond, J K. et al. BMJ 2003;327:1271-1275