An East African Perspective on the Commission's Work

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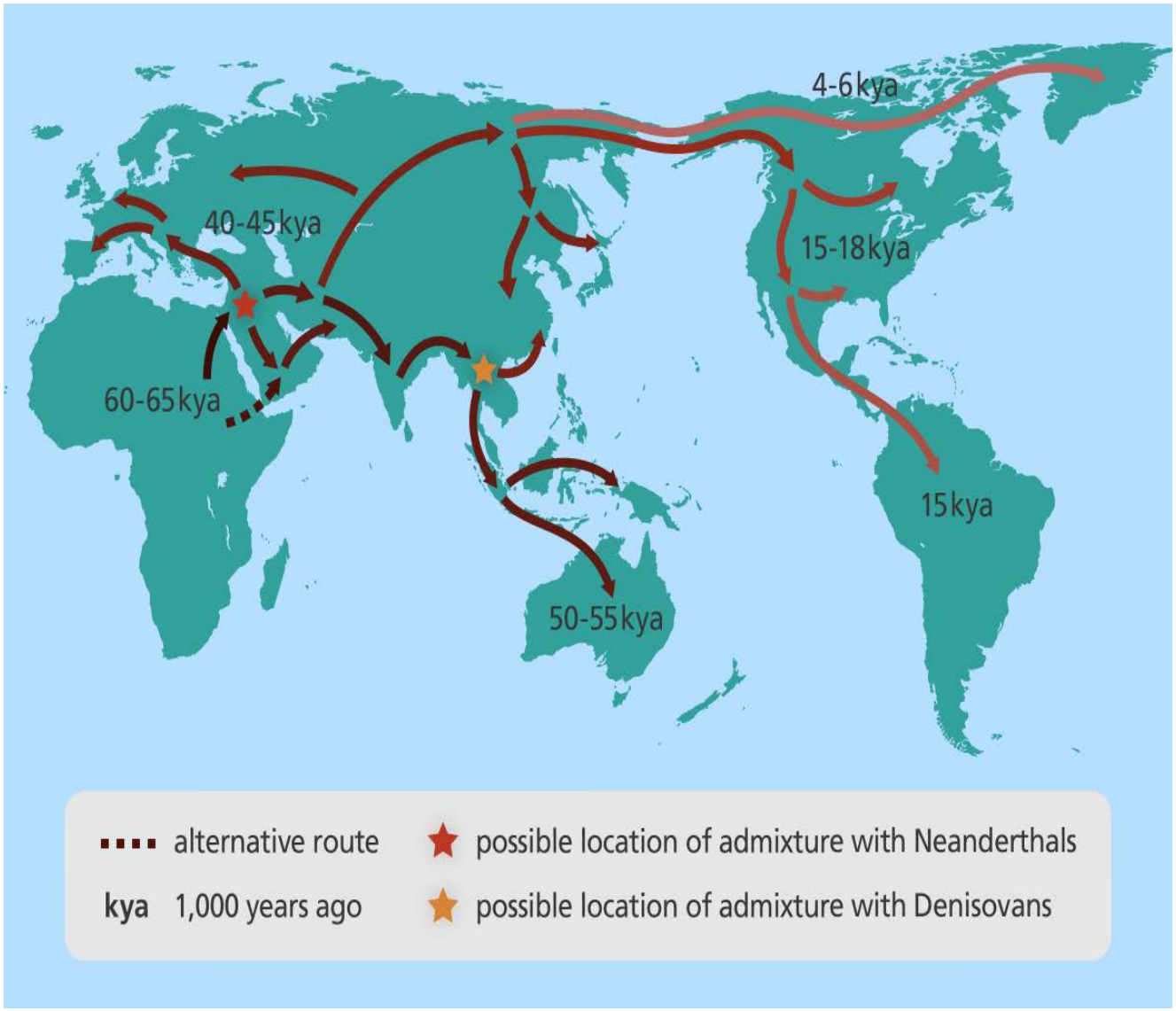
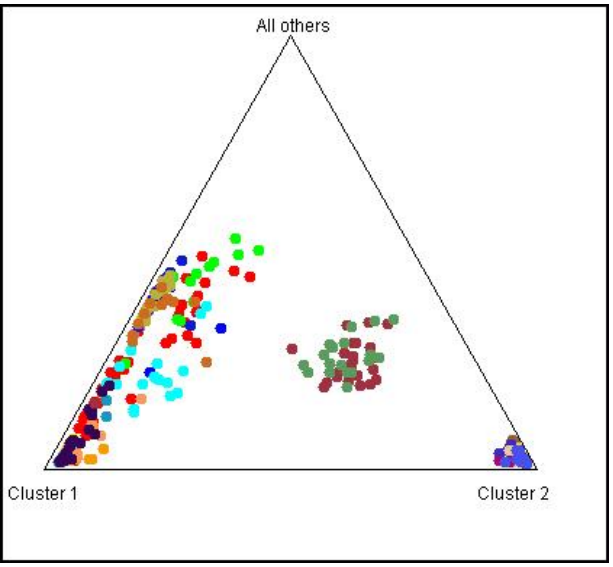
Institute of Endemic Diseases
University of Khartoum

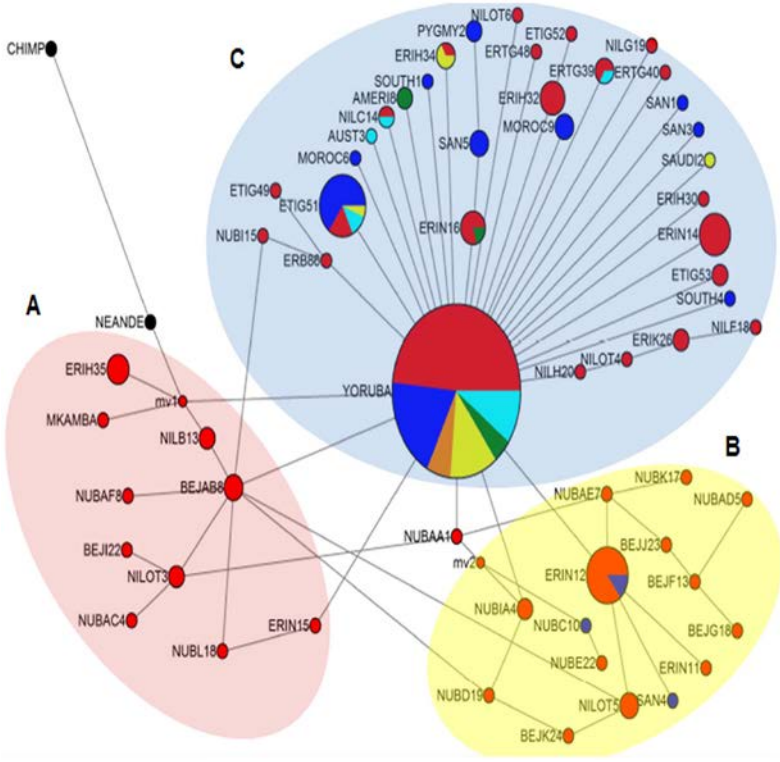
14th-16th November 2019
International Workshop of the Human Germline Genome Editing Commission

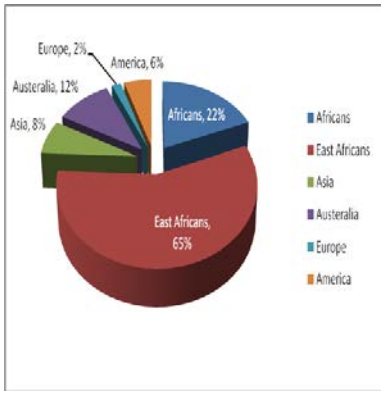
Dispersal of modern humans from Africa



✓Ancestral genomes from Africa shows close resemblance to Neanderthal genomes.







Median Joining Network based on MT-CO2 gene sequences of world populations. Black points indicate, root; Blue, East Africans; Red, Africans; Orange, Australians; Green, Asians; Pink, Americans; Purple, Europeans.

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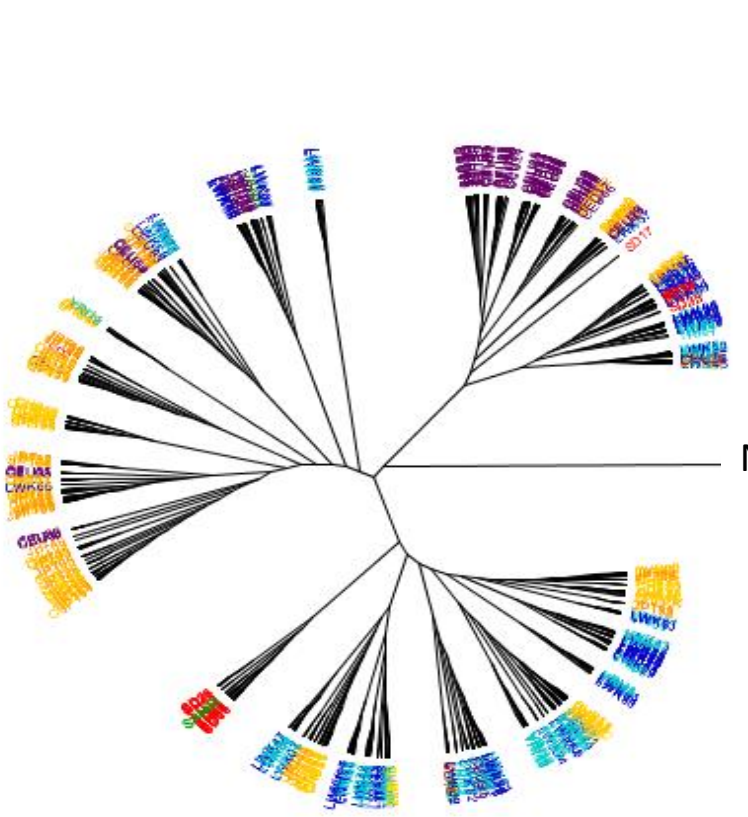
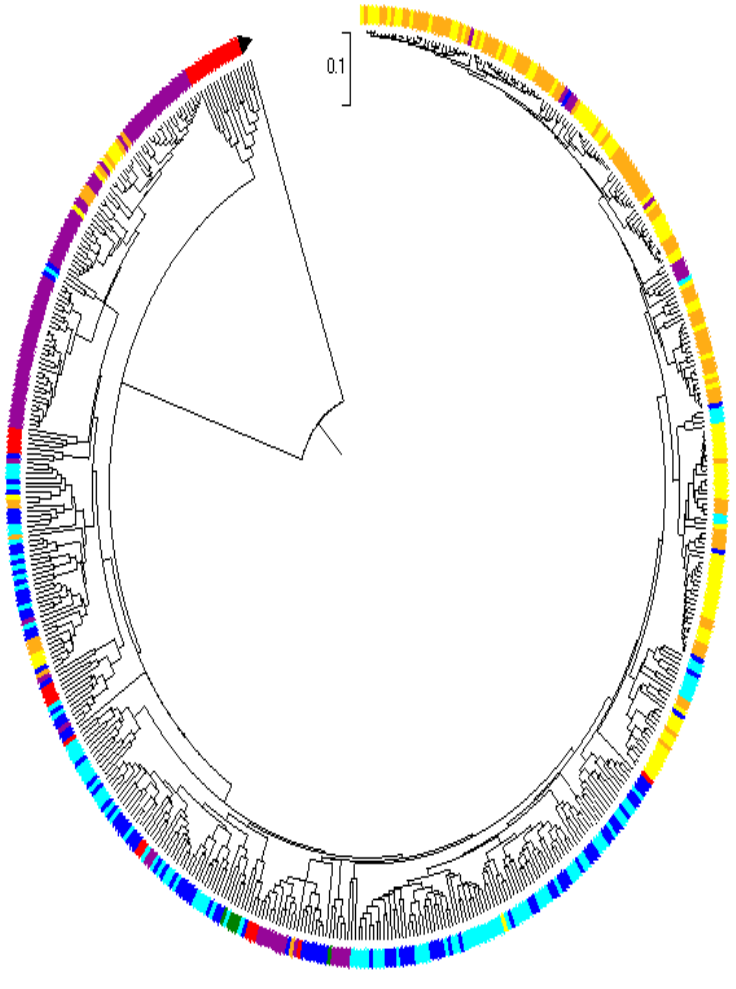
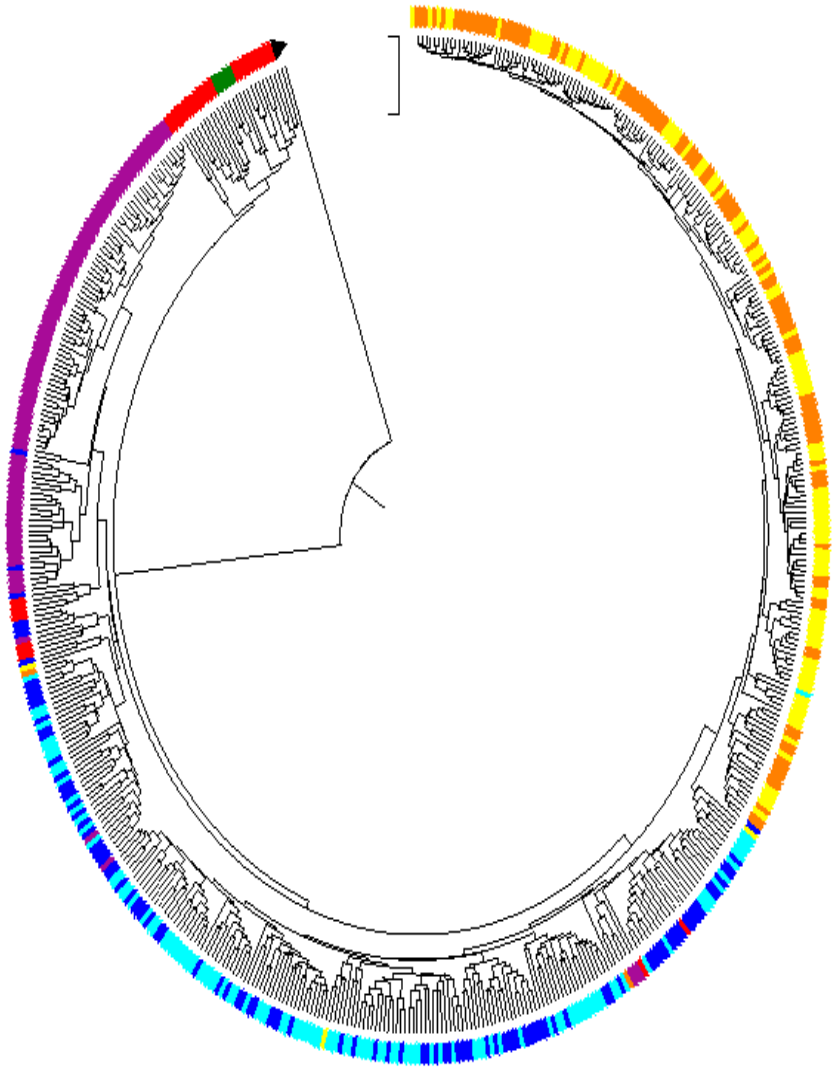
Cultural adaptive genes



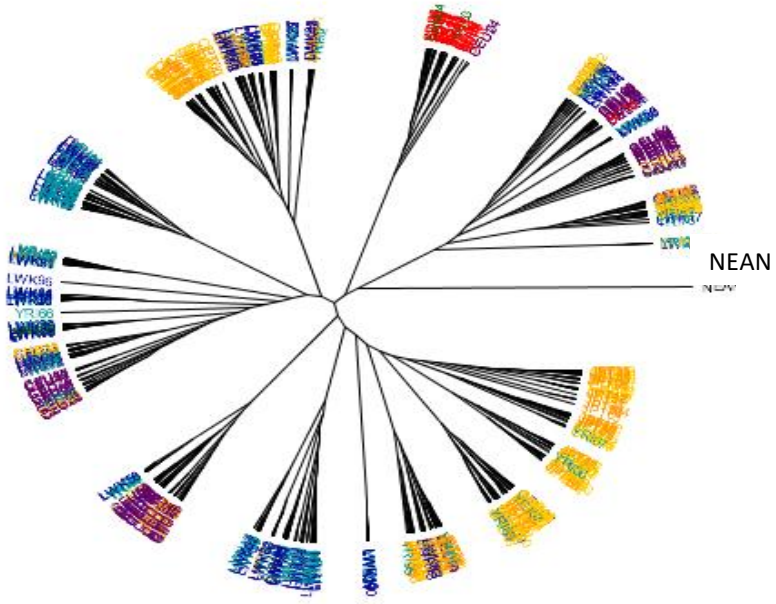


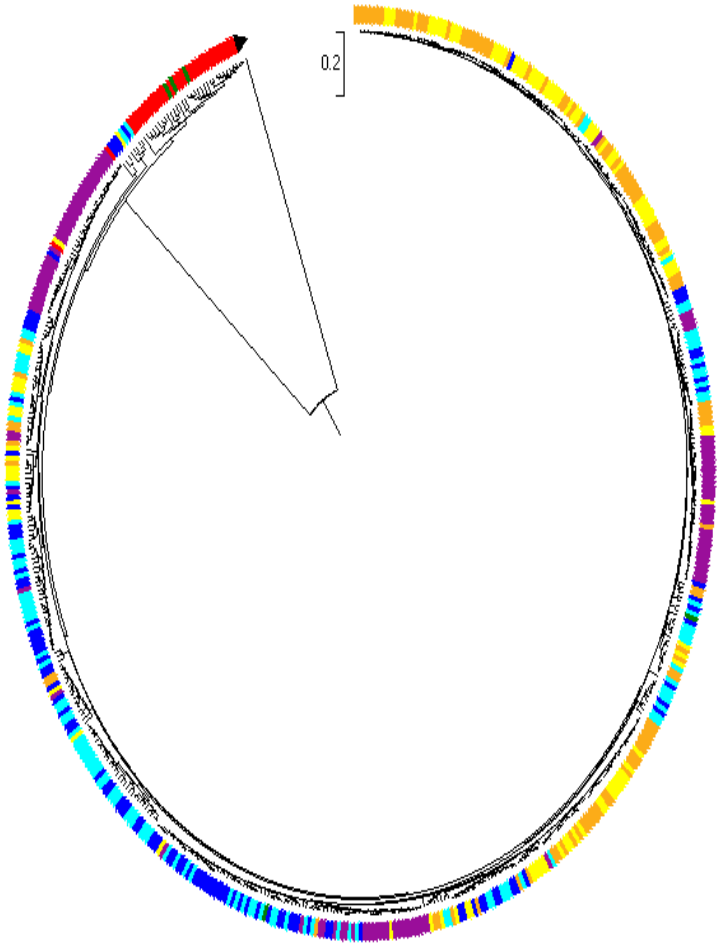
Combined variants of adaptive genes



SDN
SAN
CEU
LWK
YRI
CHB
JPT
NEAN

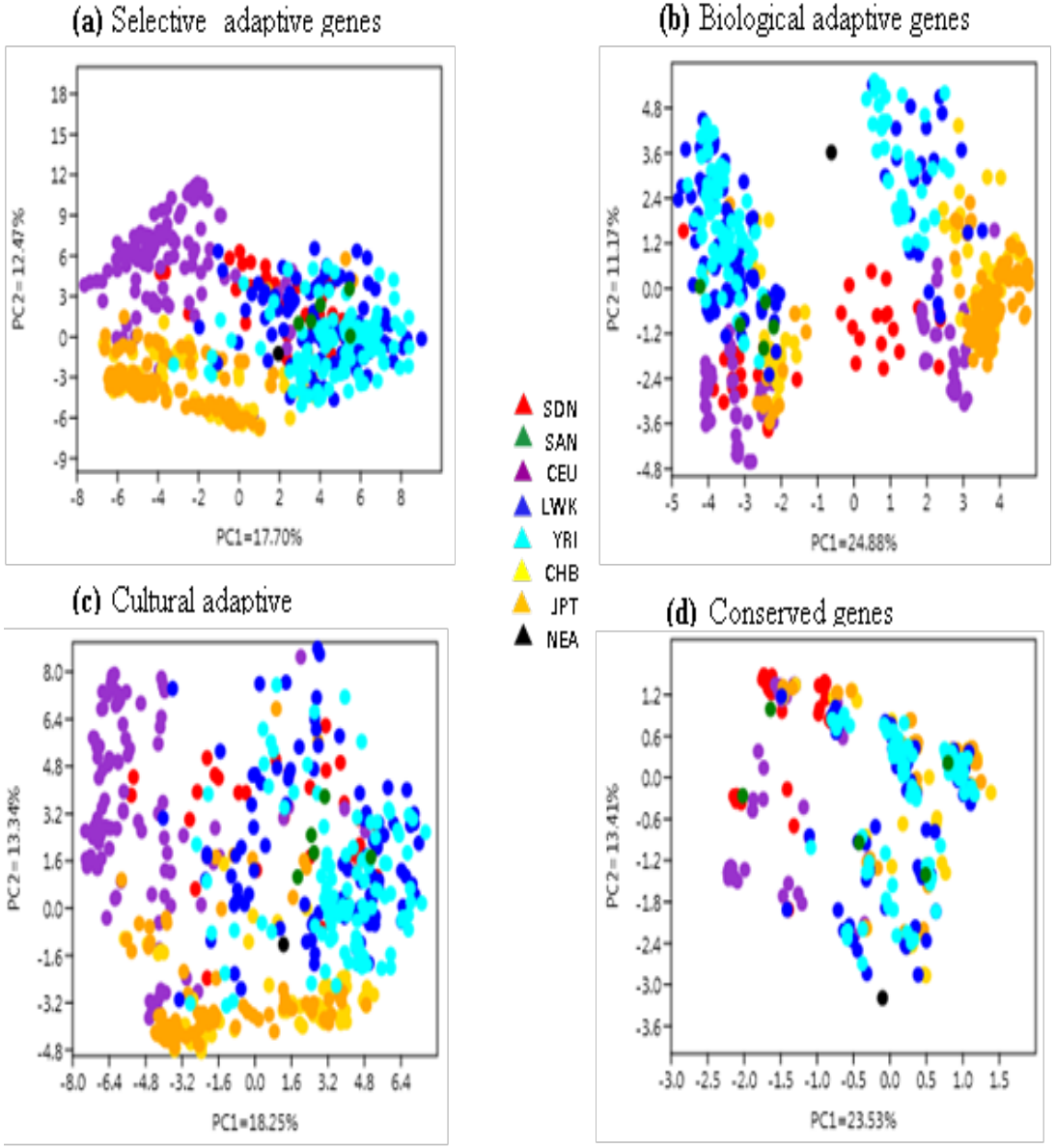
Conserved (Neutrally Adaptive) genes





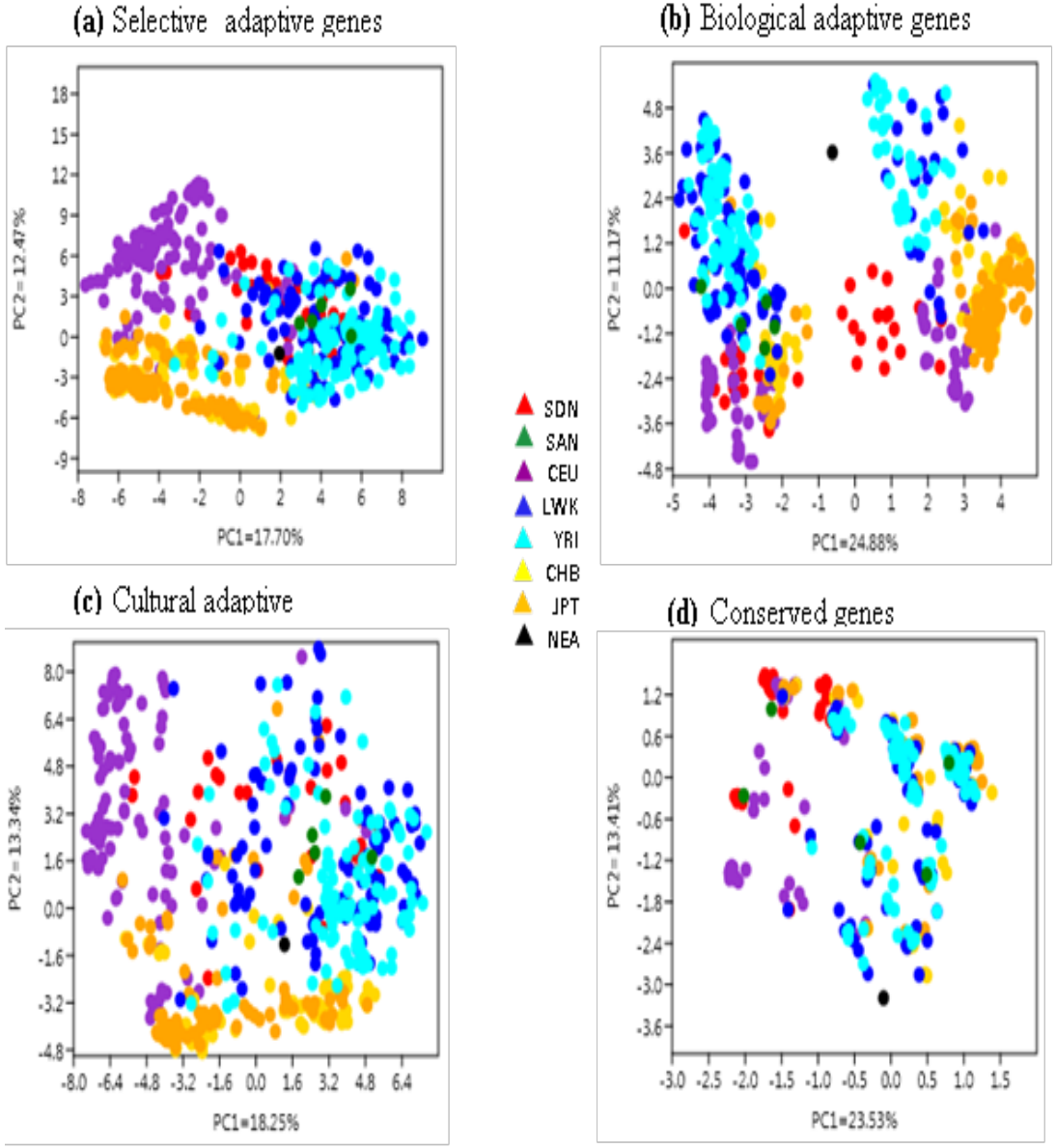
Principle Component Analysis (PCA)

The 1st and 2nd components (PC1 & PC2)



Challenges imposed by minor reference alleles on the identification and reporting of clinical variants from exome data

Mahmoud Koko, Mohammed O. E. Abdallah, M utaz Amin and Muntaser Ibrahim BMC GENOMICS



Journal of Next Generation Sequencing & Applications

Ibrahim and Musa, Next Generat Sequenc & Applic 2016, S1:008
http://dx.doi.org/10.4172/2469-9853.S1-008

Effective Size and Effectiveness: Next Generation Sequencing and the Practice of Genomics in Africa

Muntaser Ibrahim* and Mahmoud Musa

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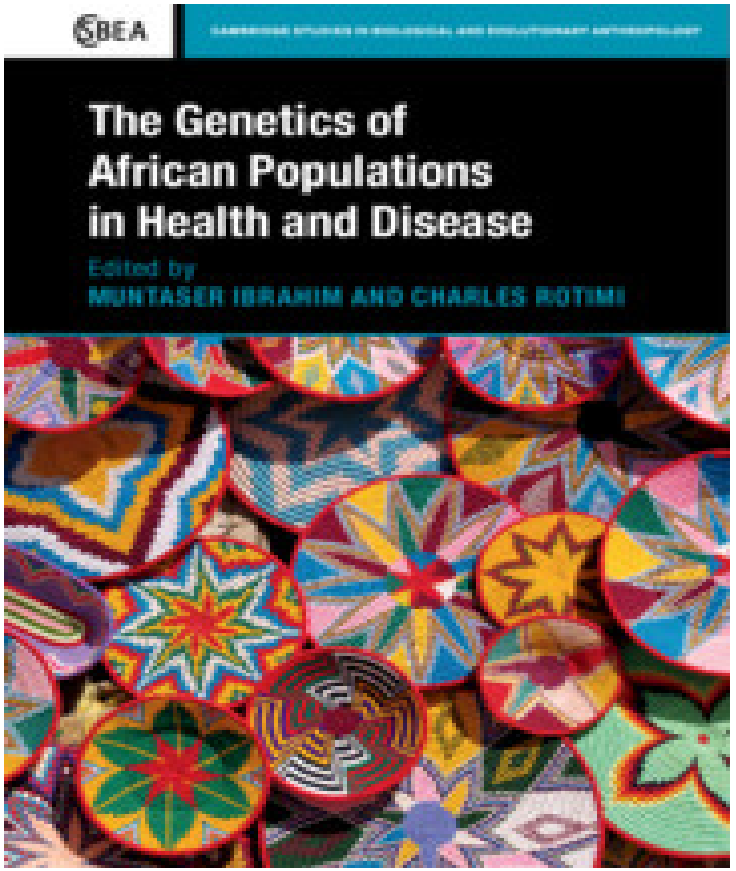
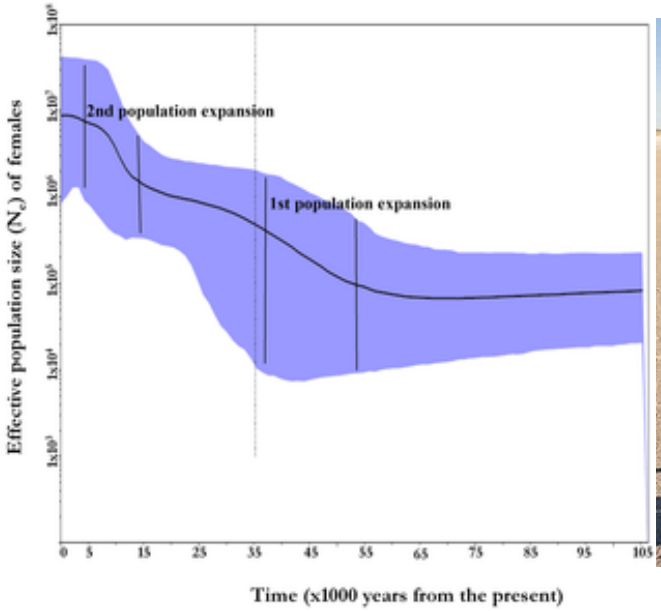
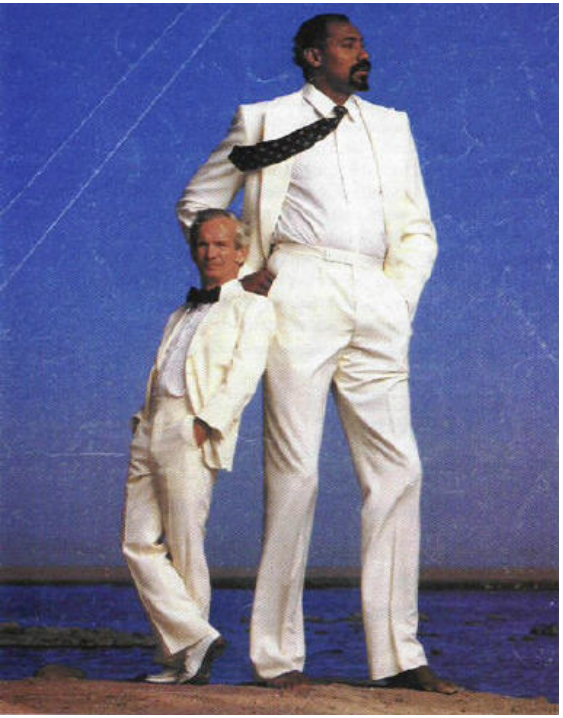
Introduction

The tremendous and unprecedented insights provided by next generation sequencing into genome functions, variations and interactions promises an enormous shift in our practice of genomics and attitude towards individual and population genetics, both in health

structure and large effective size. The premise of a putative ancestral genome that may be reconstructed from existing genomes may be flawed. Here we mention two arguments that support this: firstly, human populations in and out of Africa were influenced and shaped by drift and serial founder effects, and secondly, functional variants multiple, formed through an extended evolutionary history in Africa

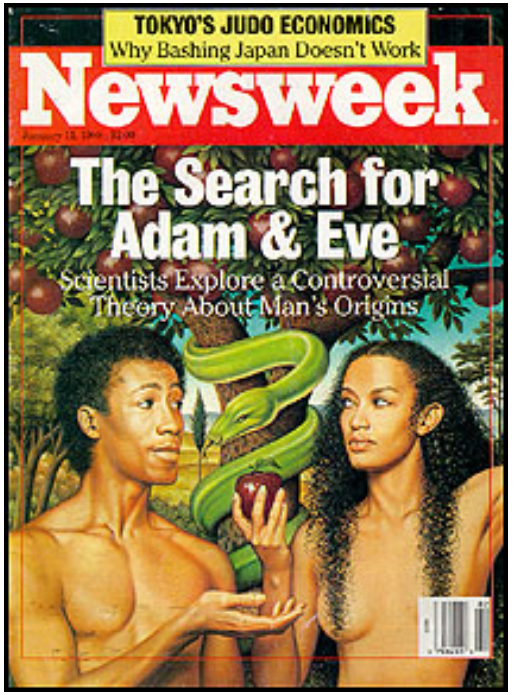


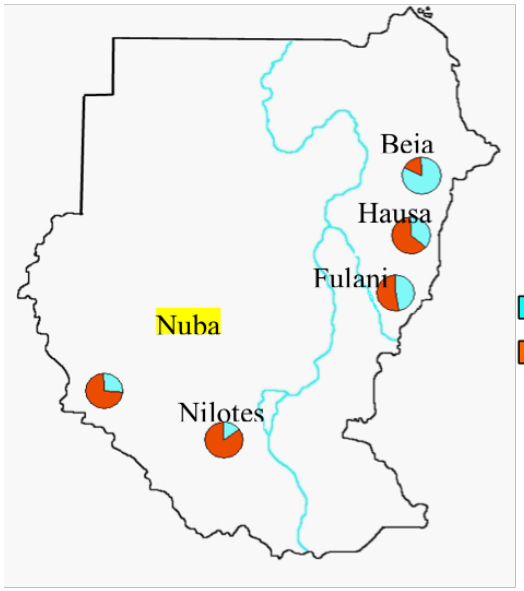




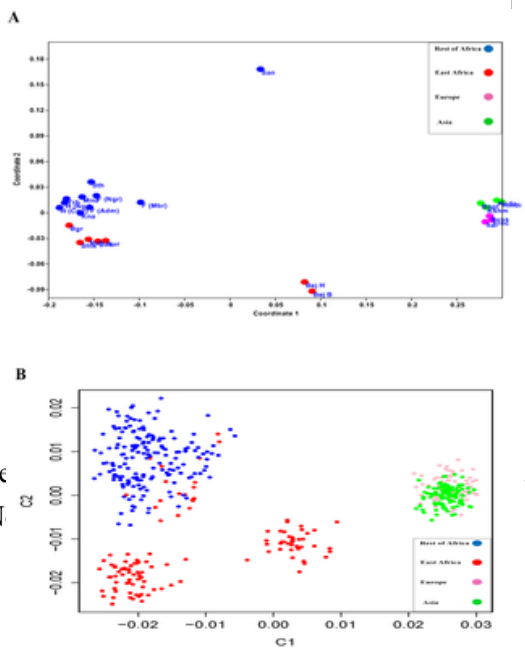
Der Brudermord.

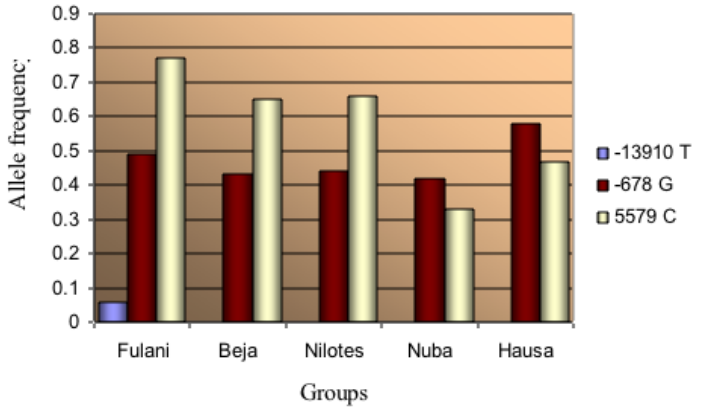
Und es begab sich, da sie auf dem Felde waren, erhub sich Cain wider seinen Bruder Abel und schlug ihn todt.
1 Mos. 4, v. 8.



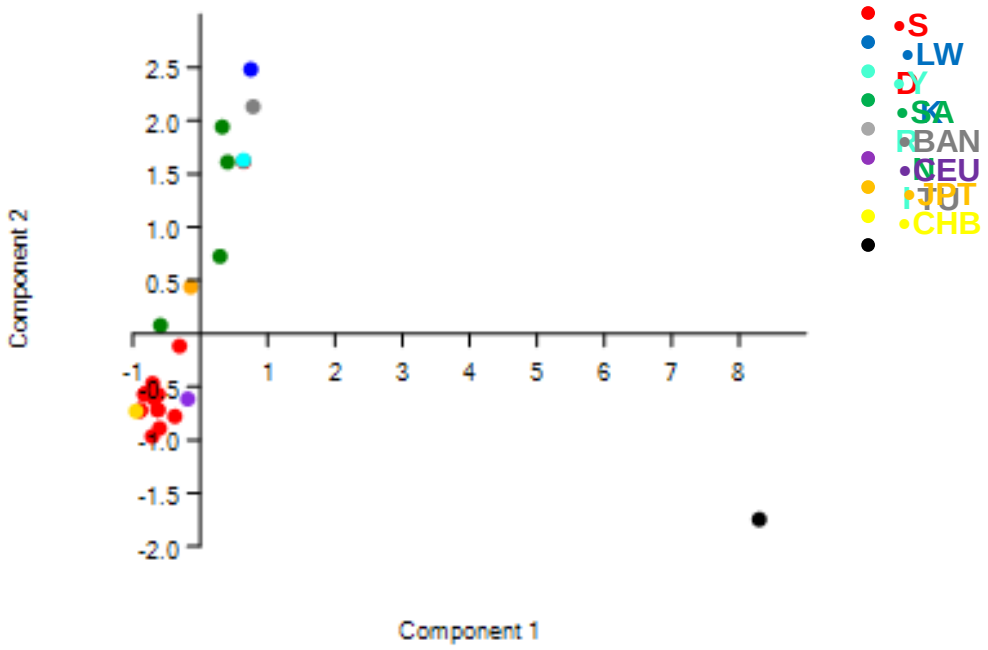


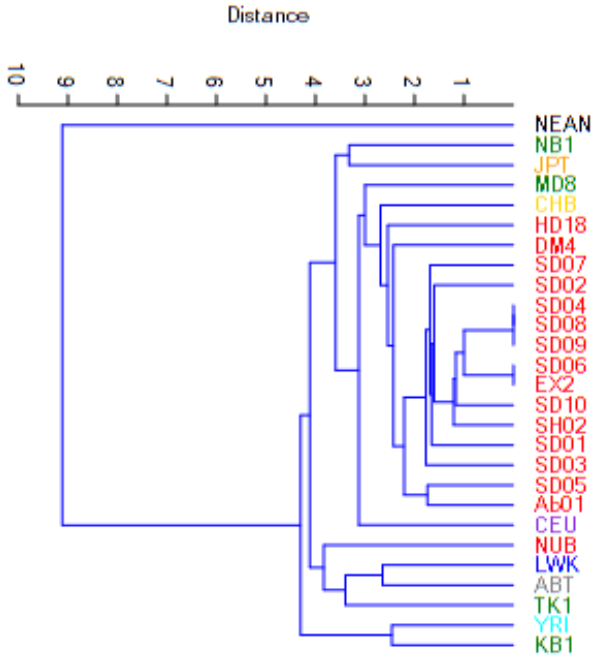
Lactase pe
Lactase N





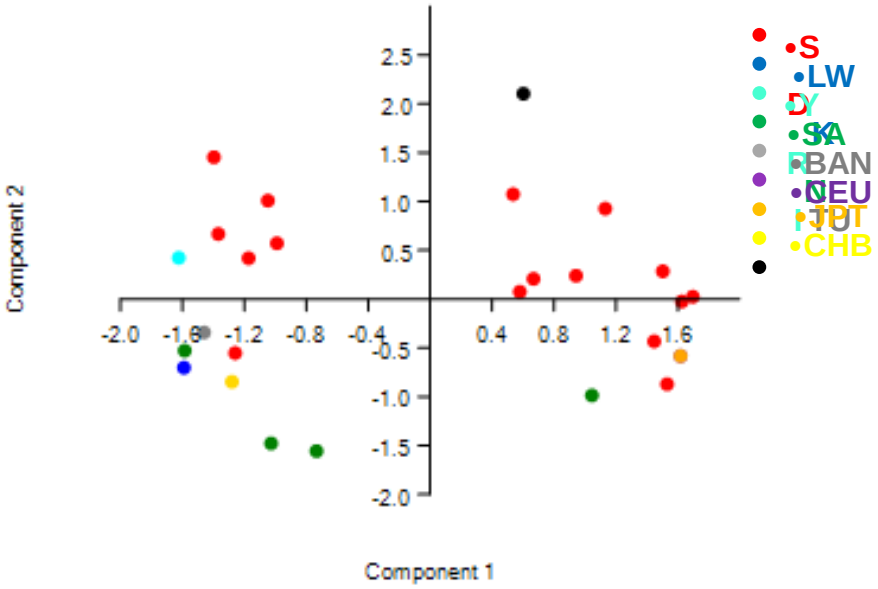
- Alcohol Adaptation
- *ADH1B*

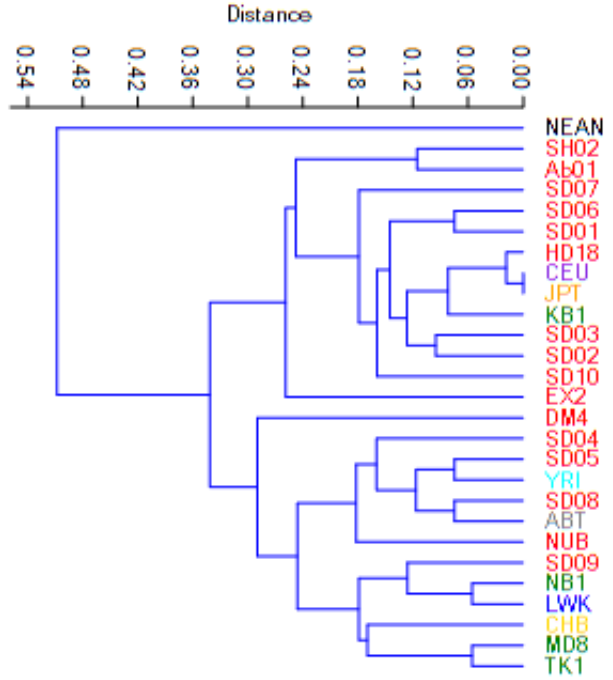


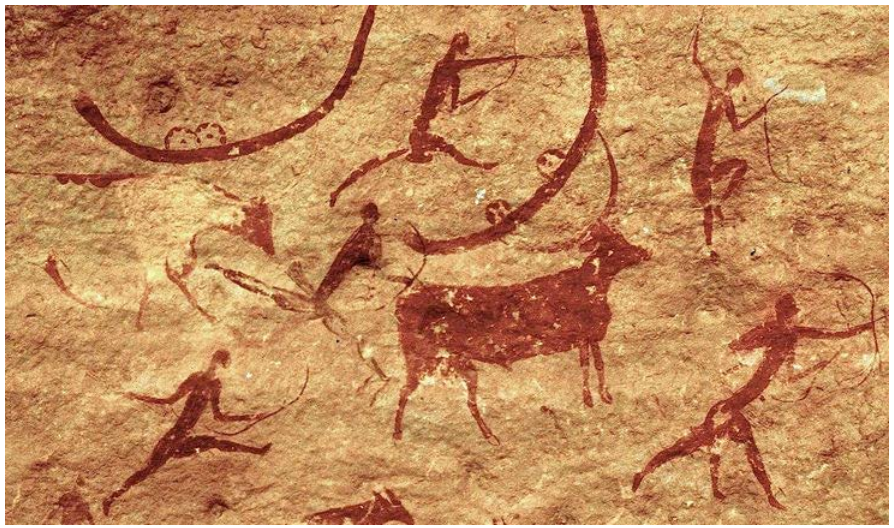


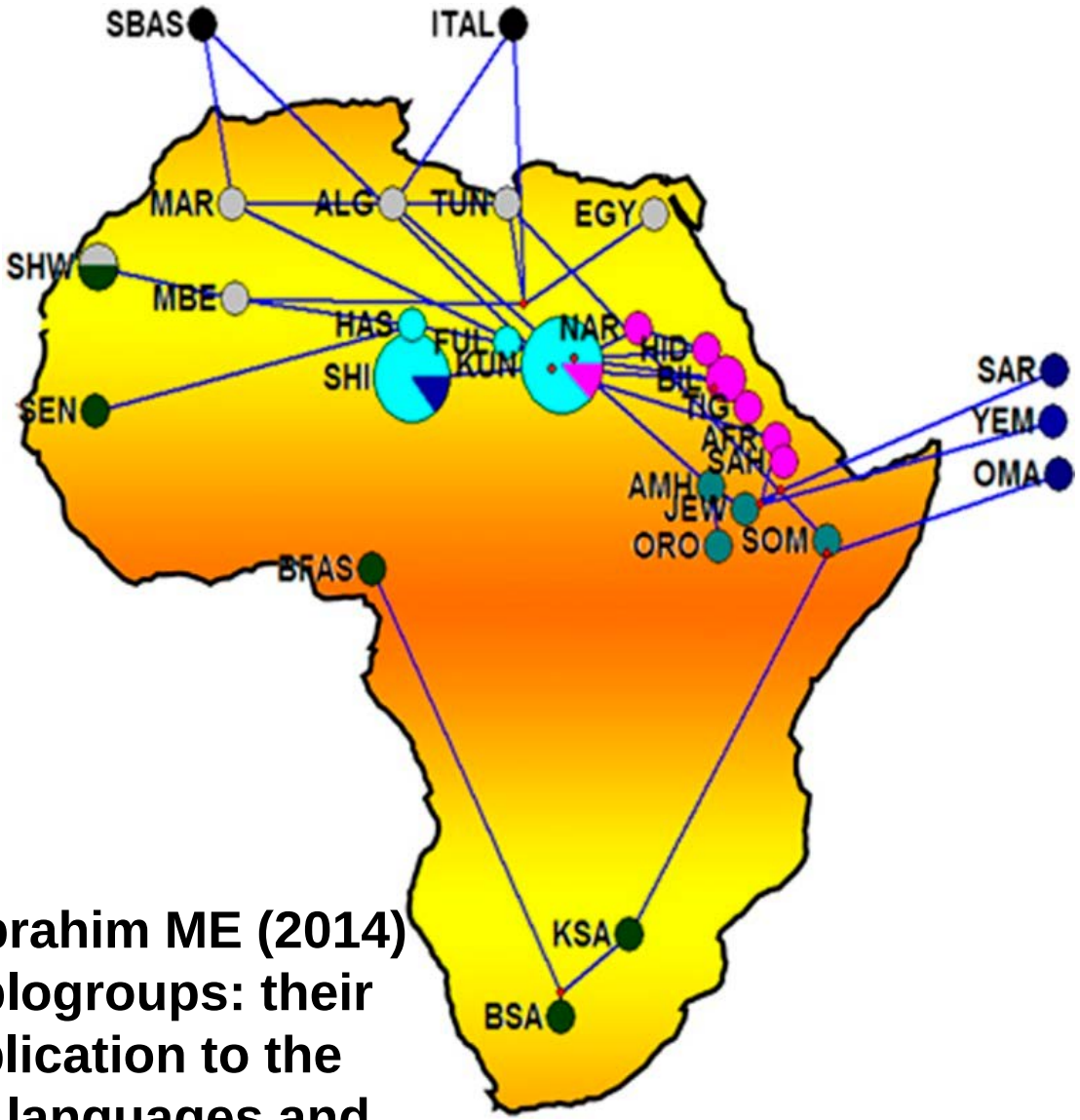
ancient

- Lactase Persistence
  - *LCT*









- **Gebremeskel E and Ibrahim ME (2014) Y-chromosome E haplogroups: their distribution and implication to the origin of Afro-Asiatic languages and pastoralism**

European Journal of Human Genetics

ext:

- Eur J Hum Genet. 2014 Dec; 22(12): 1387–1392.
- Published online 2014 Mar 26. doi: 10.1038/ejhg.2014.41

Clinical and Medical Technologies

In vitro implantation- Three Centers

Stem Cell research capacity

Clinical exome sequencing

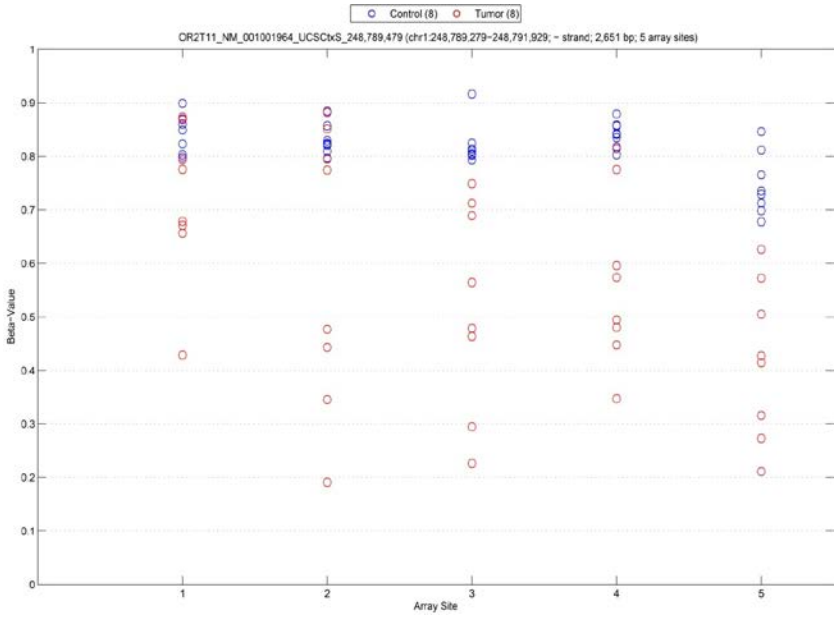
Burden of Genetic Diseases

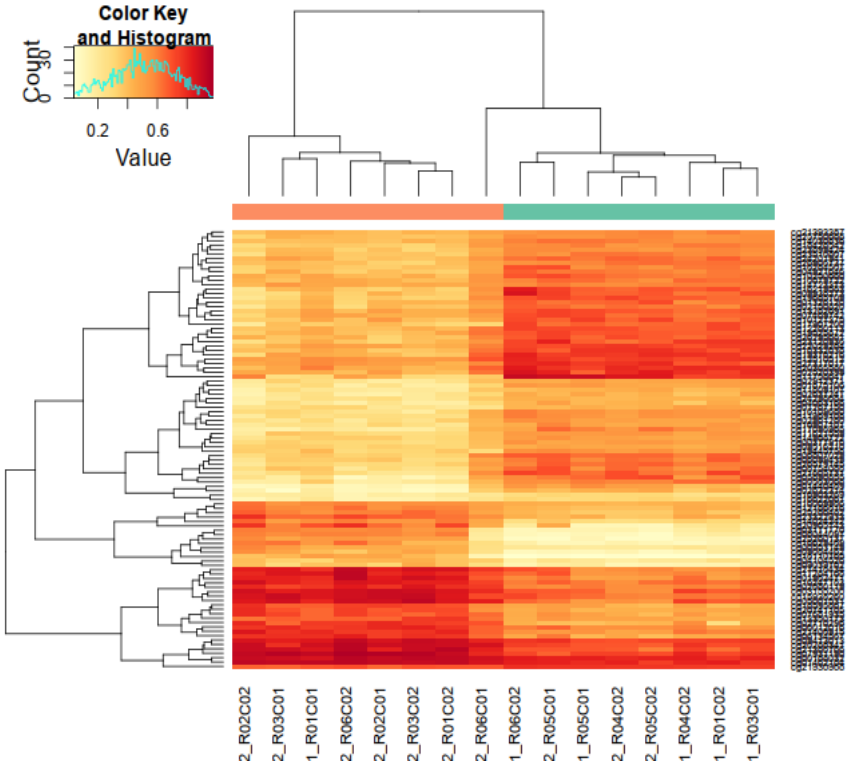
The highest frequency of Sickle Cell disease in Africa among some ethnic groups

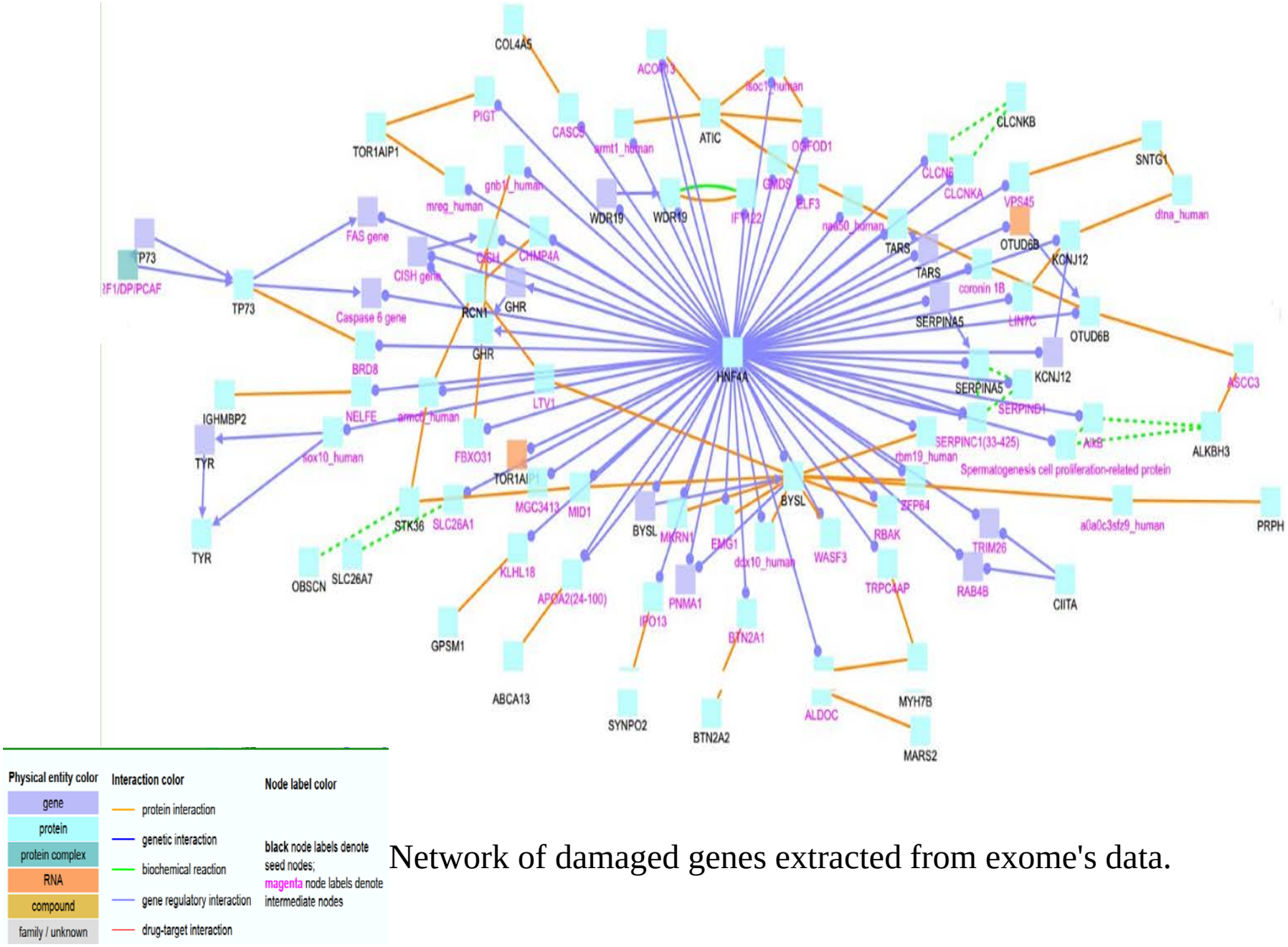
Neurological and single gene” disorder are surfacing as public health problem

Cancer is now among the top major causes of death

Whole Methylome of Breast cancer







Physical entity color

- gene
- protein
- protein complex
- RNA
- compound
- family / unknown

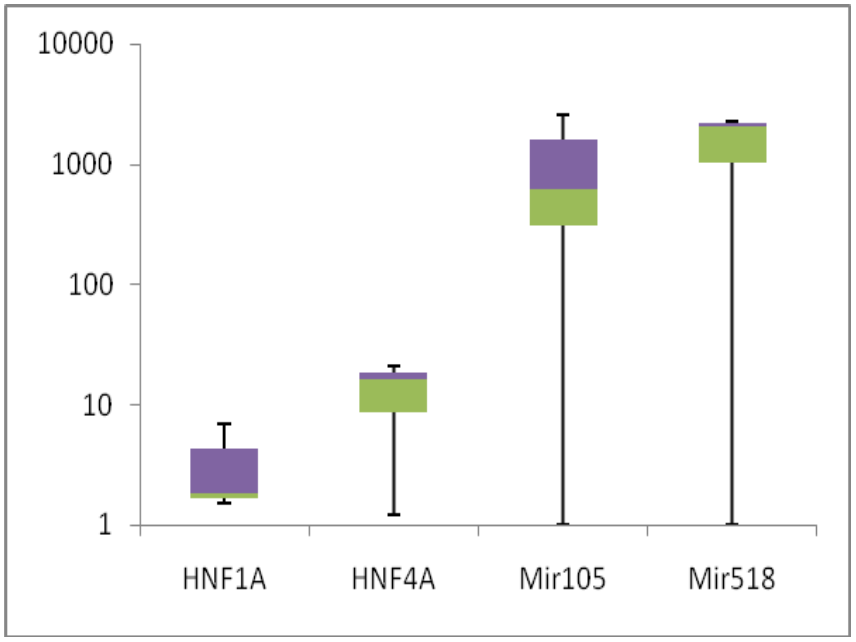
Interaction color

- protein interaction
- genetic interaction
- biochemical reaction
- gene regulatory interaction
- drug-target interaction

Node label color

black node labels denote seed nodes;
magenta node labels denote intermediate nodes

Network of damaged genes extracted from exome's data.



Box plot and Whiskers diagram show the results of fold change of the specific genes and MicroRNAs (Level of fold change for each sample).

frontiers in Genetics

ORIGINAL RESEARCH
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CrossMark

Exome sequencing of a colorectal cancer family reveals shared mutation pattern and predisposition circuitry along tumor pathways

*Suleiman H. Suleiman[1†], Mahmoud E. Koko[2†], Wafaa H. Nasir[2], Ommnyiah Elfateh[2], Ubai K. Elgizouli[2], Mohammed O. E. Abdallah[2], Khalid O. Alfarouk[2], Ayman Hussain[2], Shima Faisal[2], Fathelrahamn M. A. Ibrahim[2], Maurizio Romano[3], Ali Sultan[4], Lawrence Banks[3], Melanie Newport[5], Francesco Baralle[3], Ahmed M. Elhassan[1], Hiba S. Mohamed[1] and Muntaser E. Ibrahim[1]**

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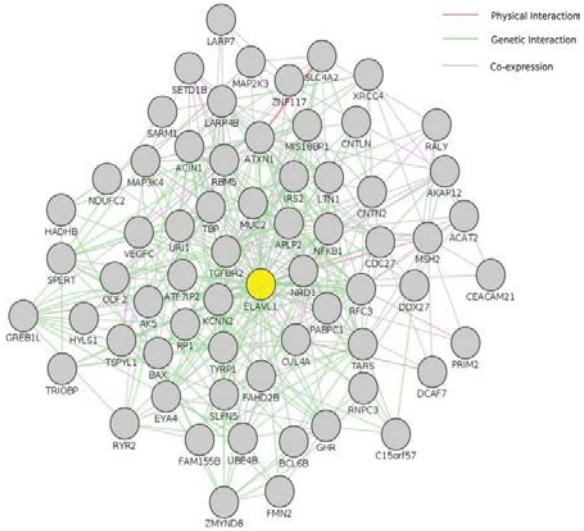
Sven Bilke,



Koko *et al. BMC Genomics* (2018) 19:46
DOI 10.1186/s12864-018-4433-3

BMC Genomics

RESEARCH ARTICLE Open Access

Challenges imposed by minor reference alleles on the identification and reporting of clinical variants from exome data

Mahmoud Koko[1,2*], Mohammed O. E. Abdallah[1], Mutaz Amin[1,3] and Muntaser Ibrahim[1*]

Journal of Molecular Biomarkers & Diagnosis

Masri, et al., J Mol Biomark Diagn 2015, S2:011
http://dx.doi.org/10.4172/2155-9929.S2-011

Commentary Open Access

In-vitro "Depletion" of Mitochondrial Cytochrome C Oxidase Subunit II Affects the Patterns of Gene Expression across Multiple Cancer Pathways

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Abstract

There is mounting molecular evidence to suggest mitochondrial malfunctions as a key element in turning-on the vicious circle of oncogenesis in the human body. Cytochrome c oxidase II (MT-CO2) encoded by mitochondrial DNA, and implicated in a number of tumors, has been shown to bind directly to cytochrome c and is speculated to regulate apoptosis through this affinity for cytochrome c. In an attempt to understand the effect of MT-CO2 depletion on the cell function we employ RNA interference and low density arrays encompassing six cancer pathways to gain insights on the potential effect on gene expression caused by siRNA specific to MT-CO2. The results show that MT-CO2 knock- down initiated differential expression in eleven genes involved in different pathways including cell cycle, signaling, apoptosis and Angiogenesis, indicating that mtDNA and sMT-CO2 in particular may be key players in the stability of the genome and its functions during tumoregensis.

Keywords: Cancer; Mitochondrial DNA; Cytochrome c oxidase subuint II; RNA interference

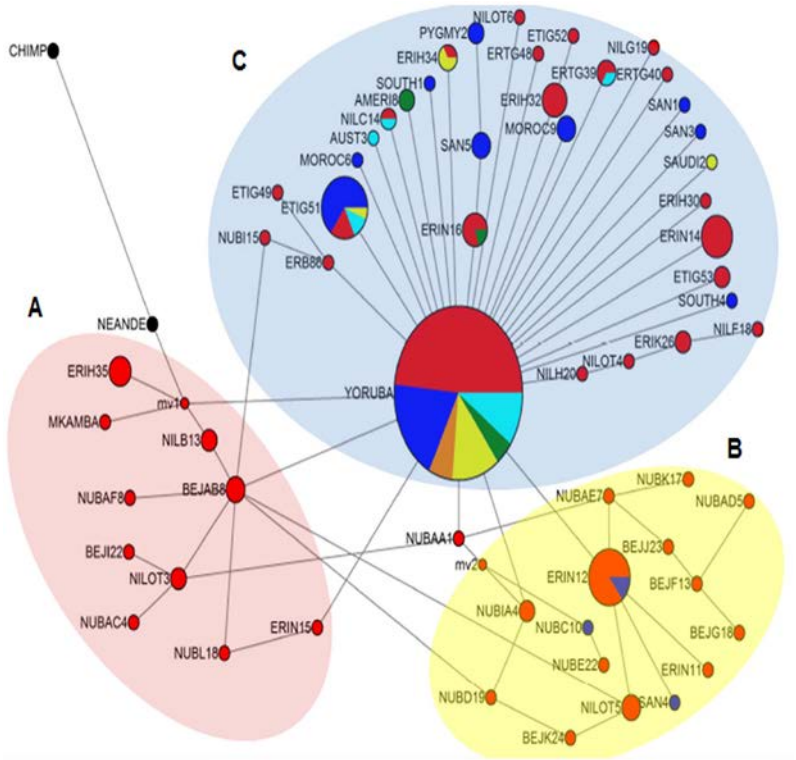
Abbreviations

ERBB2: Human Epidermal growth factor Receptor 2; APAF: Apoptotic Protease Activating Factor 1; BRCA2: Breast Cancer Gene 2; CASP8: Caspase 8; CASP9: Caspase 9; HIF1α: Hypoxia Inducible Factor-1α; MYC: Avian Myelocytomatosis Viral Oncogene Homolog; NFKB1A: nuclear factor kappa light polypeptide; PIK3CB: Phosphatidylinositol-4,5-bisphosphate 3-kinase Catalytic subunit Beta isoform; RB: Retinoblastoma Protein; S100A4: S100 calcium binding protein A4; TGFBR1: Transforming Growth Factor, Beta Receptor I; SOD2: Superoxide Dismutase 2; RAF1: RAF proto-oncogene serine-threonine/protein kinase

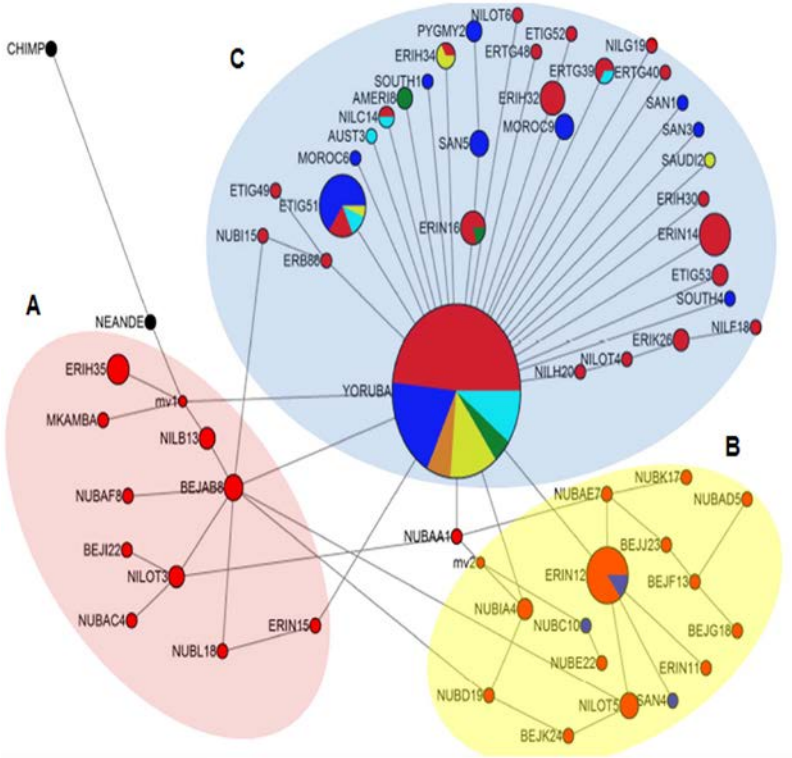
Introduction

As the enzyme at the crossroads of oxidative metabolism, cytochrome c oxidase is expected to s play a role in the Warburg effect [1]. Modulation, particularly depletion of mitochondria manifested in cytochrome c oxidase (MT-CO2) and other key enzymes has been implicated in tumorigenic transformation [2-4]. Low expression of MT-CO2 was suggested to be a marker of cancer risk in familial colon cancer [5]. Moreover, poorly differentiated colon carcinomas expresses low levels of MT-CO1 and MT-CO3, and MT-CO1 and MT-CO3 mRNAs return to higher levels when tumor cells were induced to differentiate [6]. These various qualities qualify the mitochondria and MT-CO2 to become one of the potential drug targets in cancer and other related biological dysfunctions [7]. To determine whether mtDNA depletion could be associated with malfunctions of essential genes like those involved in apoptosis or DNA repair we set an vitro system to evaluate such an effect by generating siRNA specific to the MT-CO2 knock-down.

MT-CO2 was amplified using the primer (CO2-F 5' TAGGTCTACAAG ACGCTACTT3' and (CO2 5'CTAAATCTAGGACGATGGGC 3'), BLOCK-iTTM Dicer RNAi kits (Invitrogen, catalog nos. K3600-01 and K3650-01) were used for the generation, purification, and subsequent transfection of MT-CO2-specific d-siRNA. THP-1 cell line was grown in RPMI medium supplemented with 10% fetal bovine serum in 5% CO2 and 37°C atmosphere. RNA extracted from both experimental and control THP-1 cells was treated with DNAse (Invitrogen) according to manufactures condition and then used to generate cDNA by reverse transcription (Invitrogen). Real-time quantitative PCR (qPCR) was then used to assess transfection efficiency. The difference between test and control was defined as DCt (sCt –Ct). The larger the DCt the lesser COXII expression the sample had. Each analysis was done in duplicate. The mean value of DCt was calculated for test and control and was an indicator of the level of MT-CO2 expression. The 2–ΔΔCT method was used to calculate a normalized expression change between the means of control and test samples. For low density arrays, probe was prepared using 2 µg of RNA extracted from experimental and control THP-1 cells. Hybridization was conducted using manufactures conditions (cDNA GEArray Q Series kit). The signal was visualized using Chemiluminescent detection kit (Phototope-Star detection Kit, BioLabs, Cat. #7020S) according to manufactures instructions. The membrane plotted with 95 genes (Table 1) was then subjected to X-ray, film was developed and scanned. Both test and control cells expression values were normalized with the house keeping gene. Spot intensities were measured and compared using ImageJ (1.42q) in both experimental and control array. Spots were then normalized according to the positive control's signal and background was subtracted using negative control area intensities as mean.



Evolutionary conservation of RNA editing in the genus Lycohemus



To what extent is the technology discussed

A lot, Masters in Molecular Medecine and Msc Molecular Biology

Young Scientists are apt and open to new technologies

Factors influencing attitude towards the technology

Ethical consierations (though might be a way out from the quandery of aborti

Often evolutionary thinking

- Thank You