

Dispatches from the mitochondria  
Dispatches from the mitochondria

**2 BYA**

**Eukaryotes**

**500 MYA**

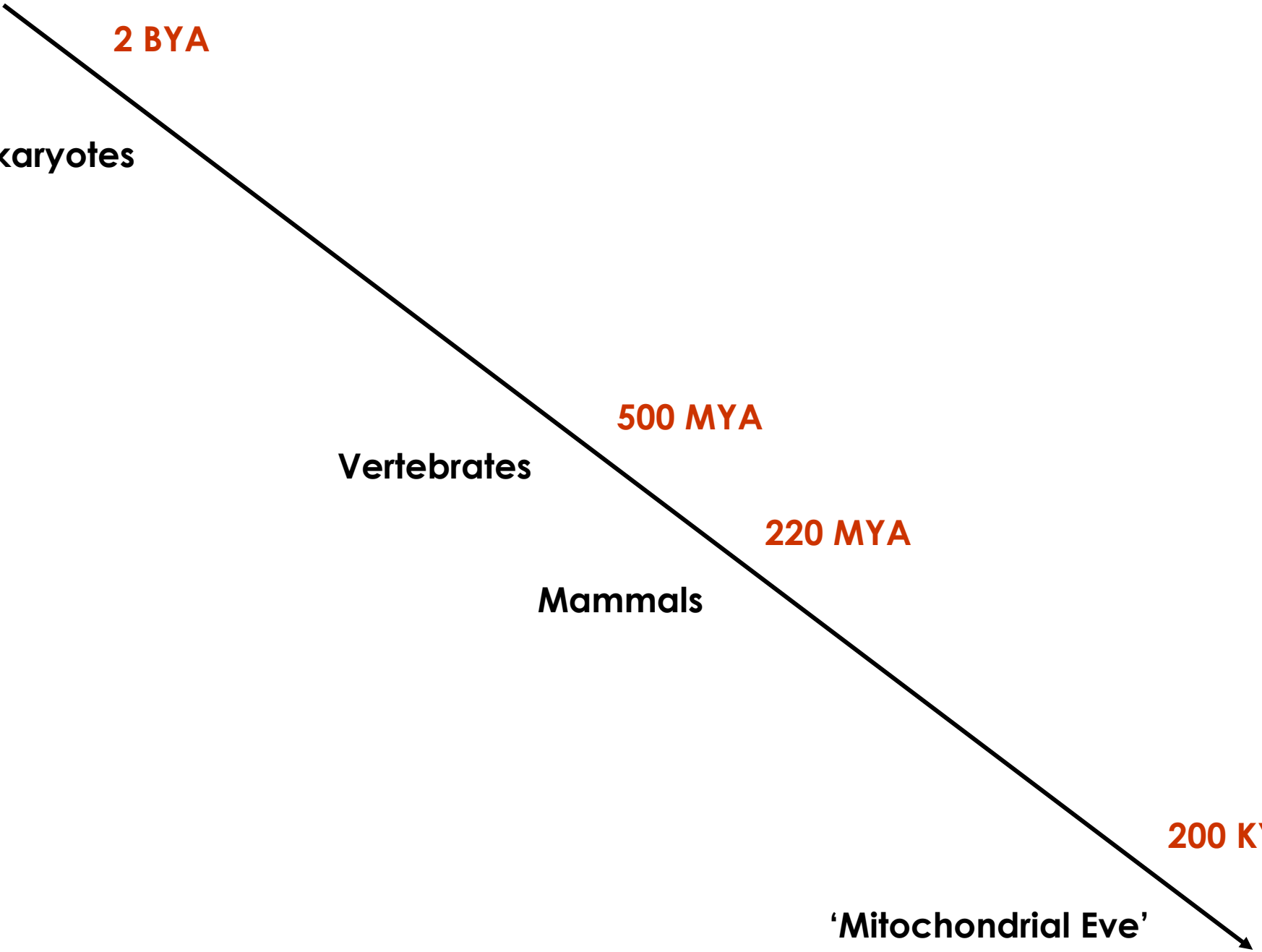
**Vertebrates**

**220 MYA**

**Mammals**

**200 KYA**

**'Mitochondrial Eve'**

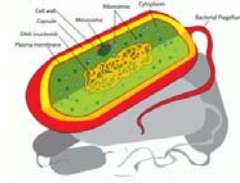


**2 BYA**

**Proto-mitochondrion**



**Archaeobacterium**



**Eubacterium**

**500 MYA**

**Vertebrates**

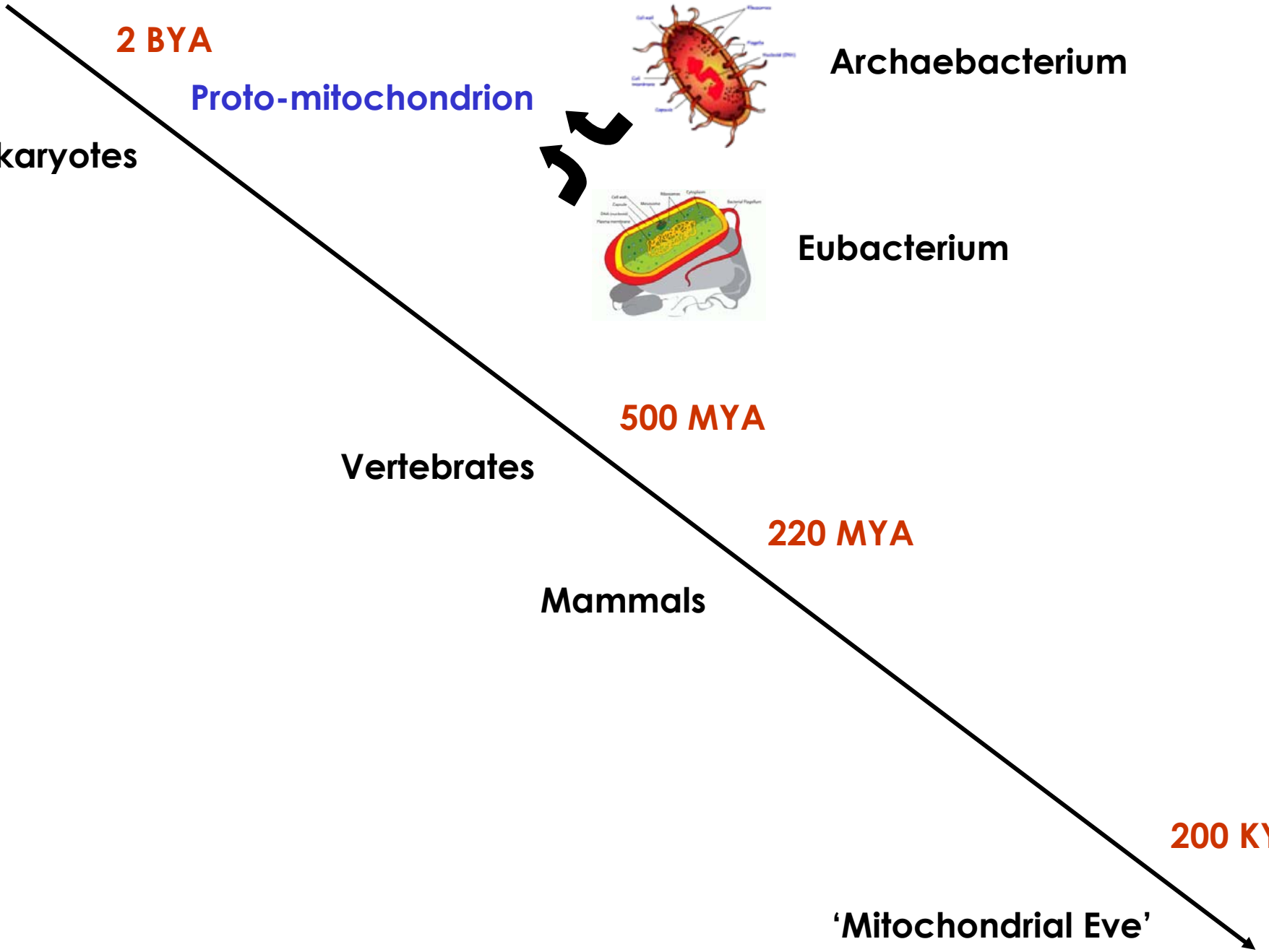
**220 MYA**

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**Eukaryotes**



**2 BYA**

**Eukaryotes**

**500 MYA**

**Vertebrates**

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**Mammals**

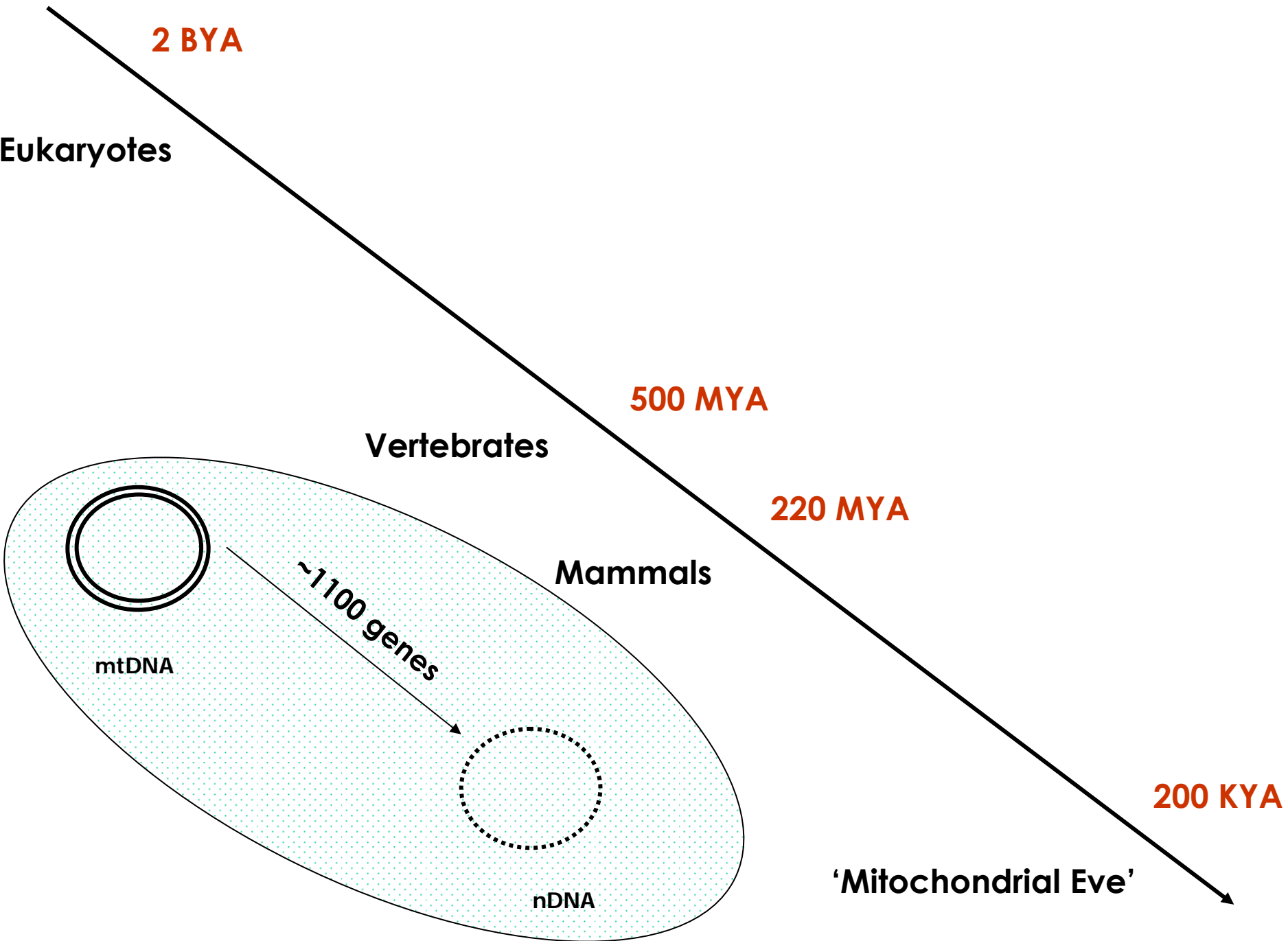
**200 KYA**

**'Mitochondrial Eve'**

mtDNA

**~1100 genes**

nDNA

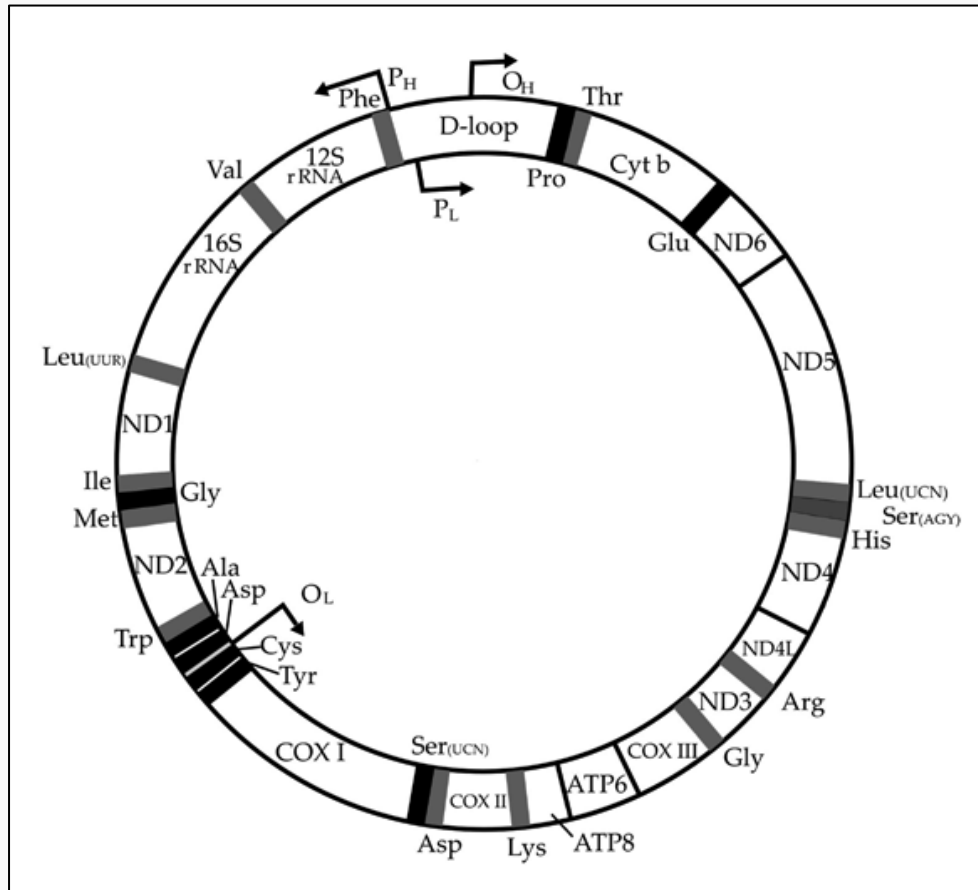


Over 90% of the functional mitochondrial genome is encoded in the nucleus.

The majority of genes encoded by the mtDNA are crucial for the machinery that converts metabolic energy into ATP.

MtDNA is maternally inherited and does not recombine.

mtDNA effects may depend on nuclear genetic background.



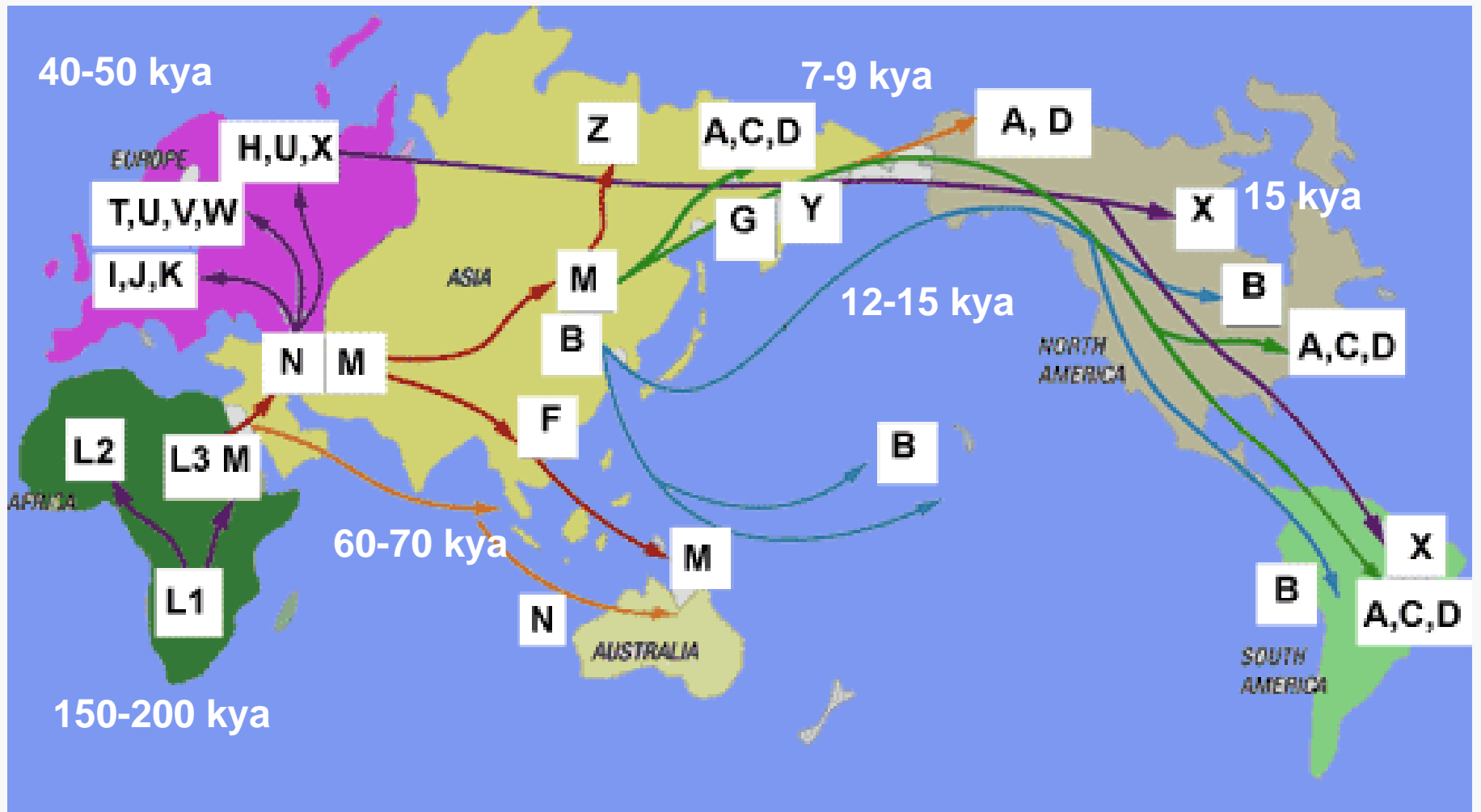
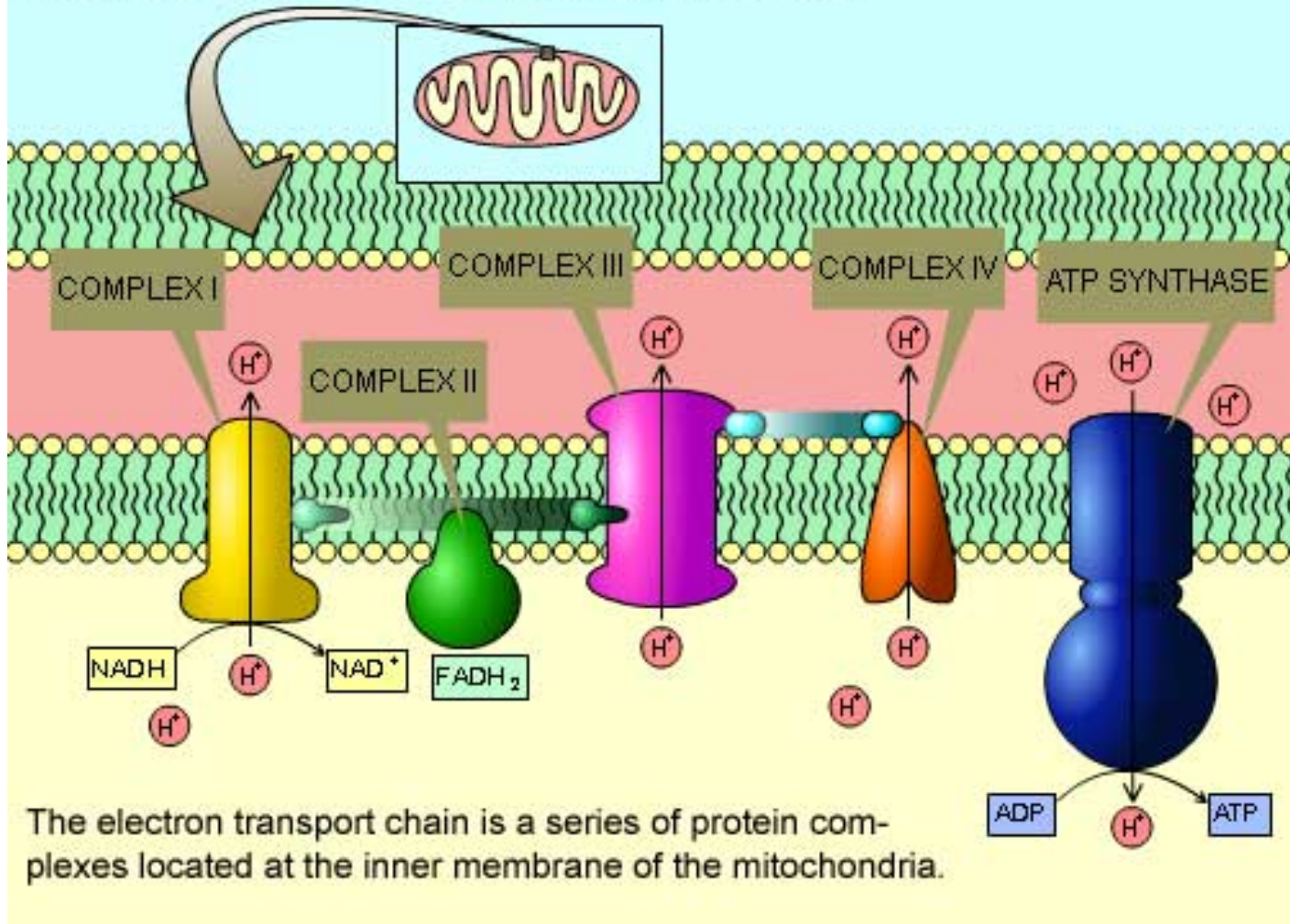


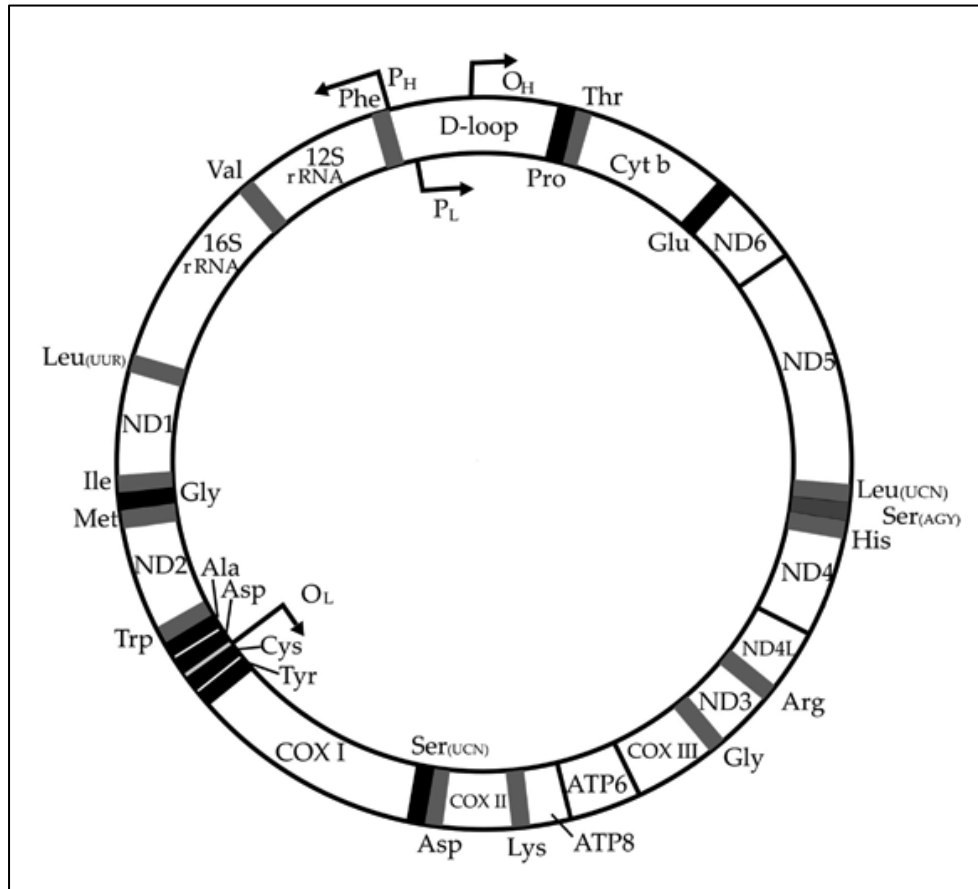
Figure J-13: Electron Transport Chain



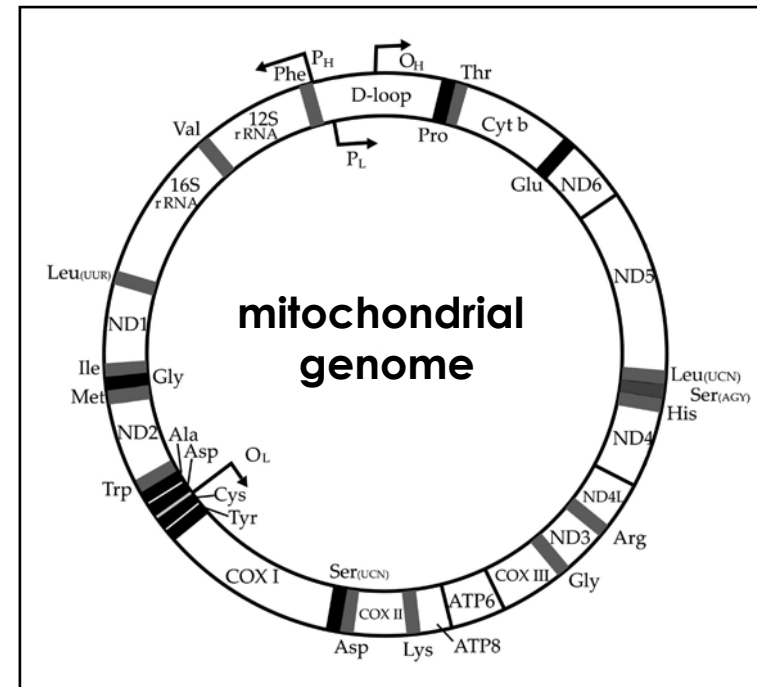
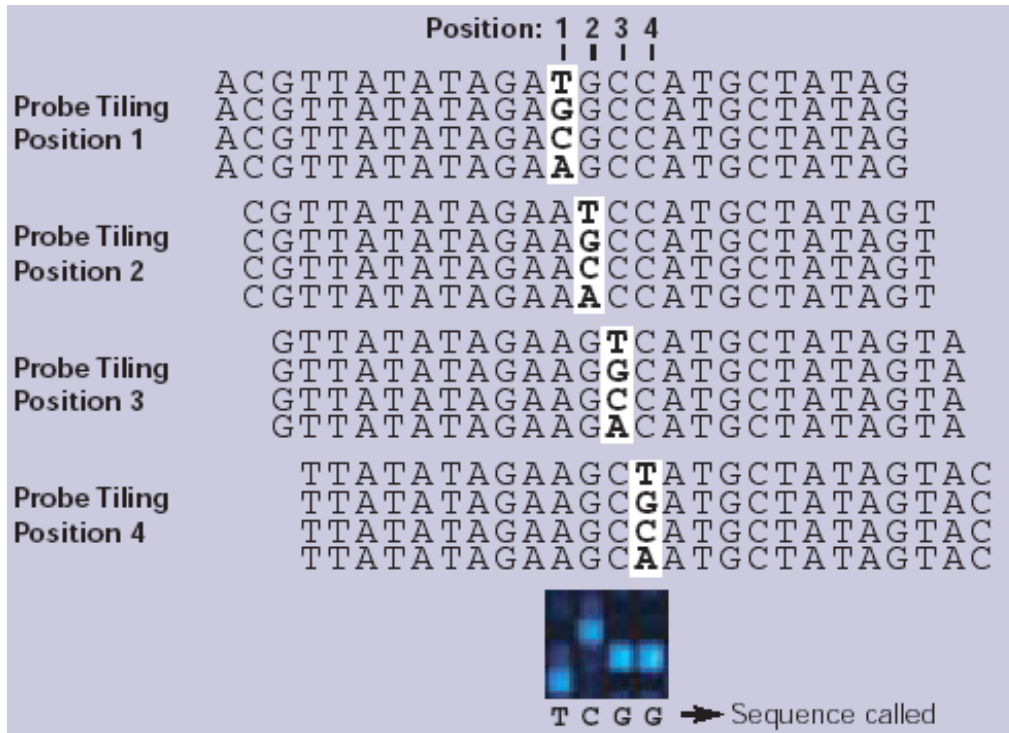
|                     | Complex I | Complex II | Complex III | Complex IV | Complex V |
|---------------------|-----------|------------|-------------|------------|-----------|
| Nuclear genes       | 39        | 4          | 10          | 10         | 12        |
| Mitochondrial genes | 7         | 0          | 1           | 3          | 2         |

# Strategies for analyzing mtDNA genotype and sequence data

- Common variation, minor allele frequency  $\geq 5\%$  including haplogroups
- Rare variation, minor allele frequency  $< 5\%$  including singletons
- Heteroplasmy

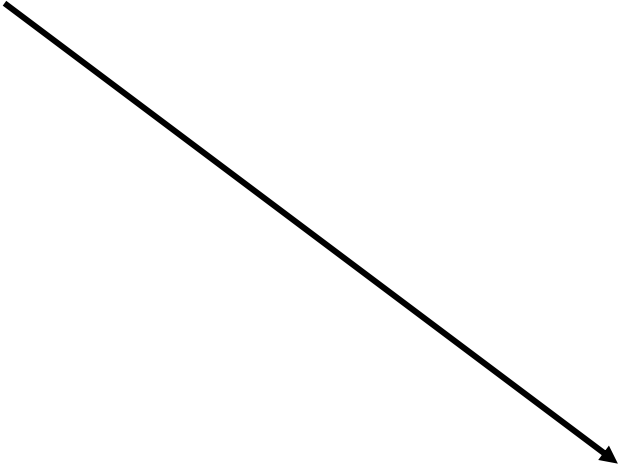


# Affymetrix MitoChip



- Principle: Allele Specific Oligonucleotide Hybridizations
- 25-mer oligonucleotides
- 4 probes/position
- ~30,000 bases of double stranded sequence
- Redundant probe tiling for detecting the major human mitochondrial haplotypes and known disease-related mutations

**Energetics**



**Mortality**

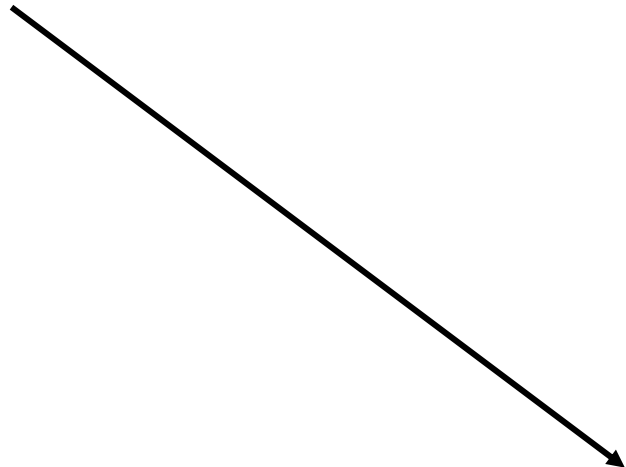
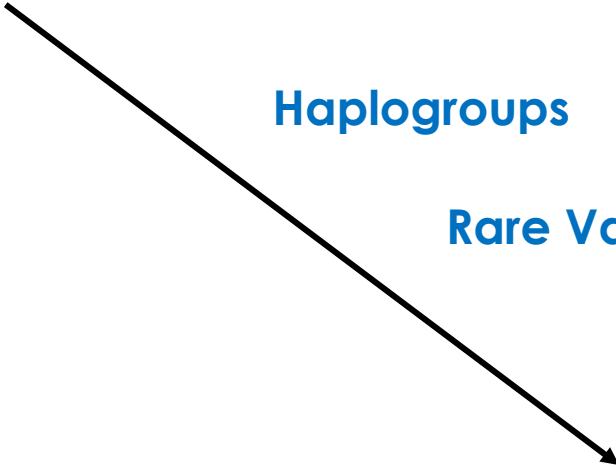
**mtDNA**

**Haplogroups**

**Rare Variants**

**Energetics**

**Mortality**



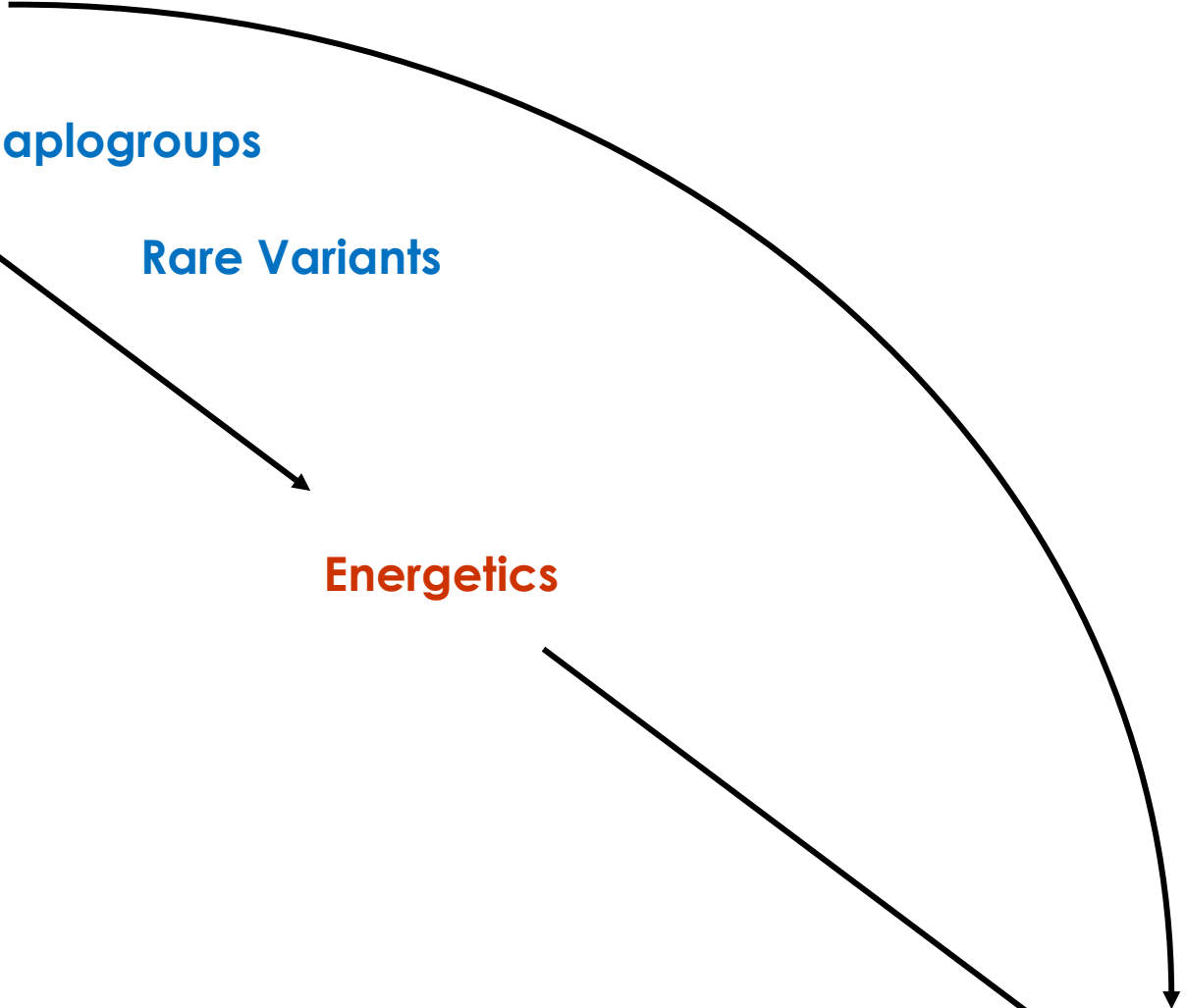
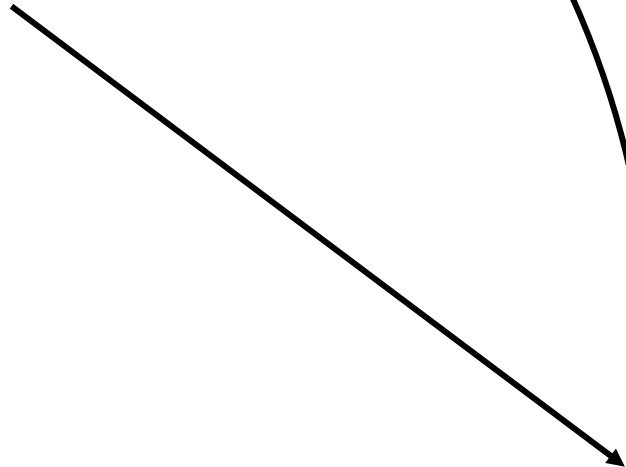
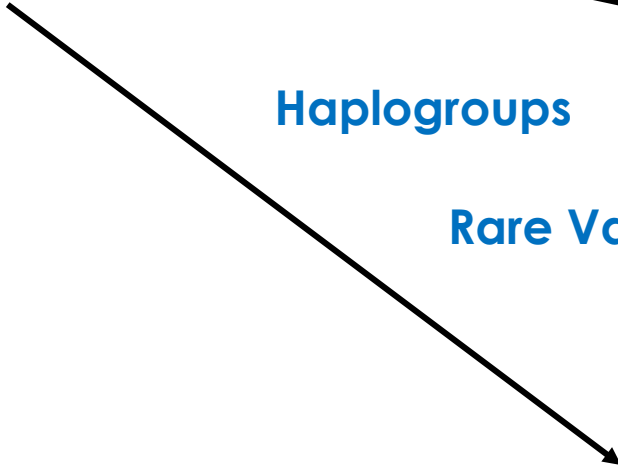
**mtDNA**

**Haplogroups**

**Rare Variants**

**Energetics**

**Mortality**



**mtDNA**

**Haplogroups**

**Rare Variants**

**Body Composition**

**Physical Performance**

**Inflammation**

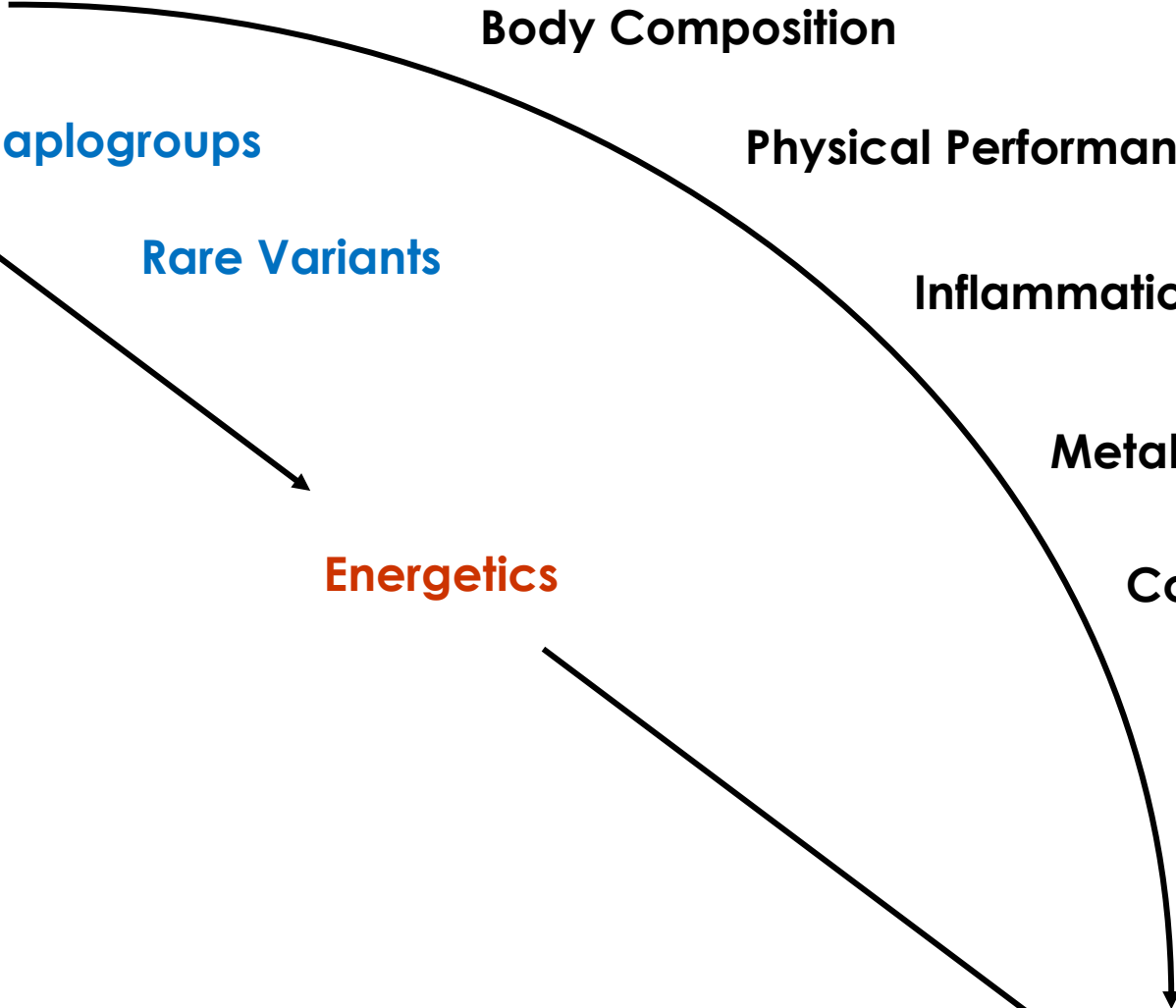
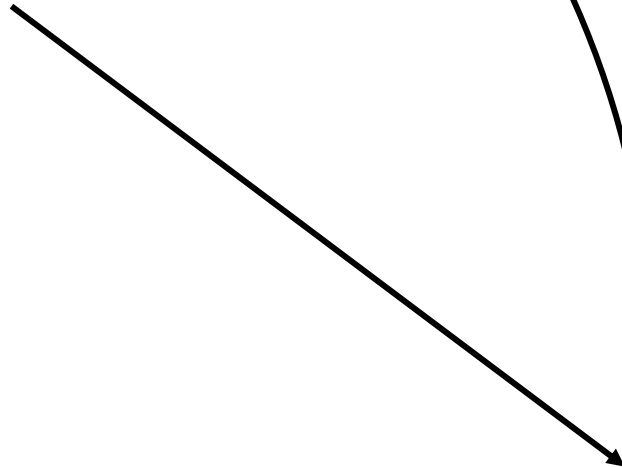
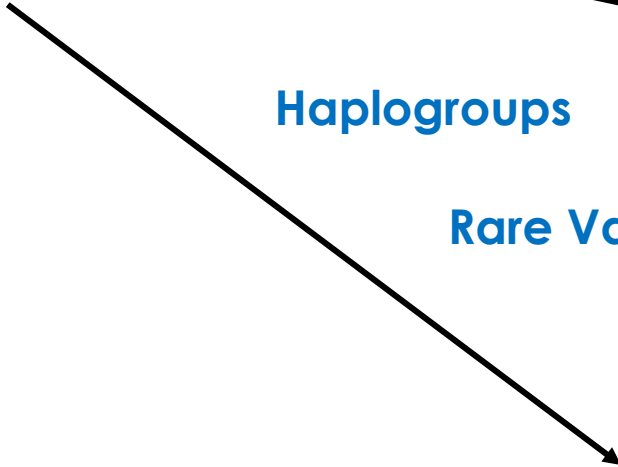
**Metabolism**

**Cognition**

**Disease**

**Energetics**

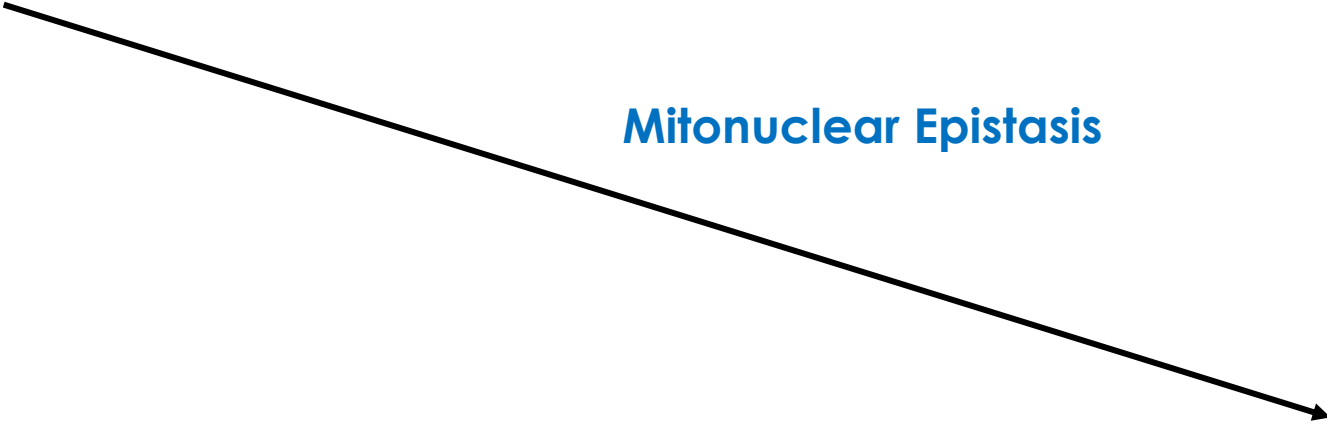
**Mortality**



**mtDNA**

**Mitochondrial Epistasis**

**Metabolism**



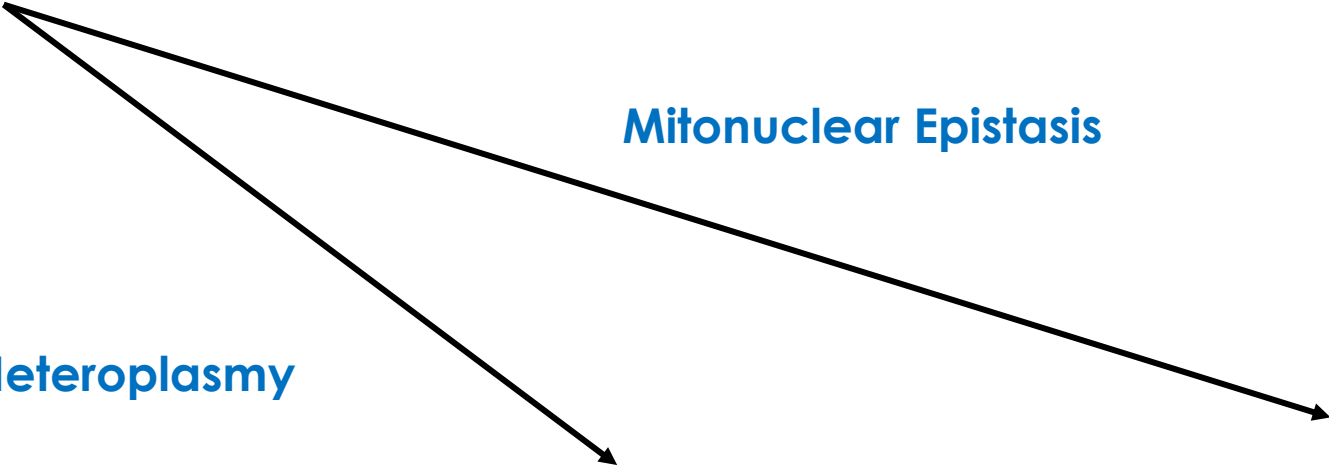
**mtDNA**

**Mitochondrial Epistasis**

**Heteroplasmy**

**Energetics**

**Metabolism**



# Health, Aging and Body Composition Study

Energetics substudy (n~300) Manini et al. JAMA, July 12, 2006—Vol 296, No. 2

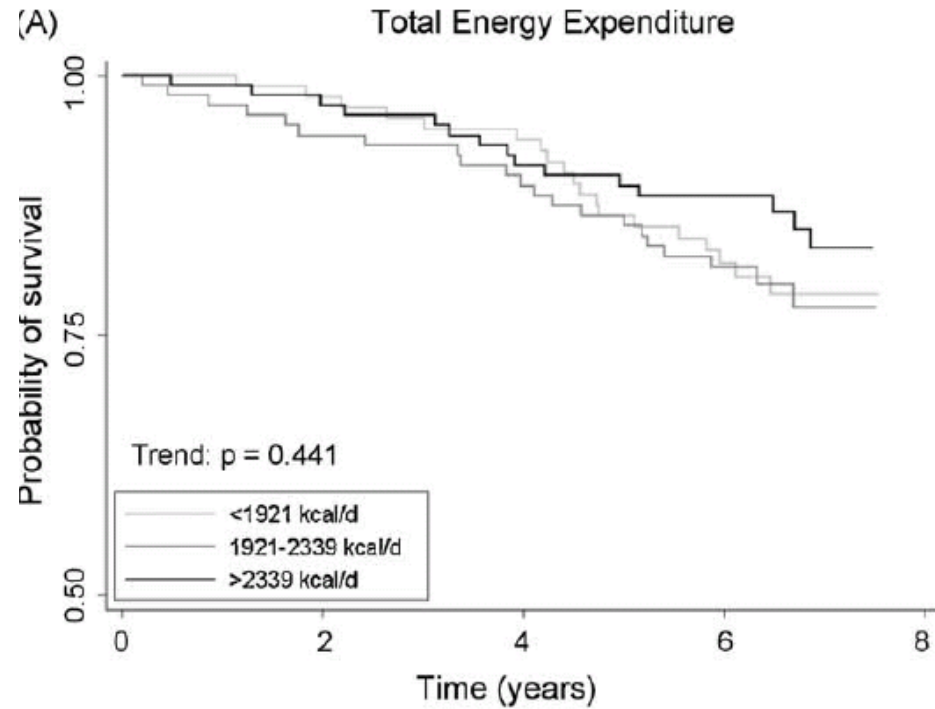
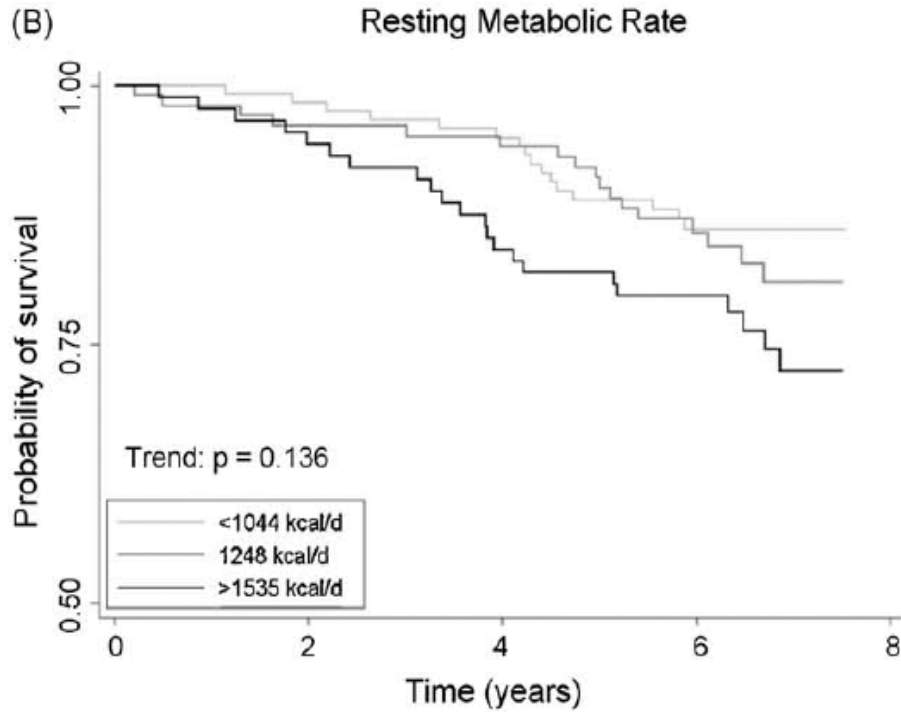
## Resting metabolic rate

Indirect calorimetry on a Deltatrac II respiratory gas analyzer (Datex Ohmeda Inc, Helsinki).

## Total energy expenditure

2-point doubly labeled water technique.

# Health, Aging and Body Composition Study



# Health, Aging and Body Composition Study

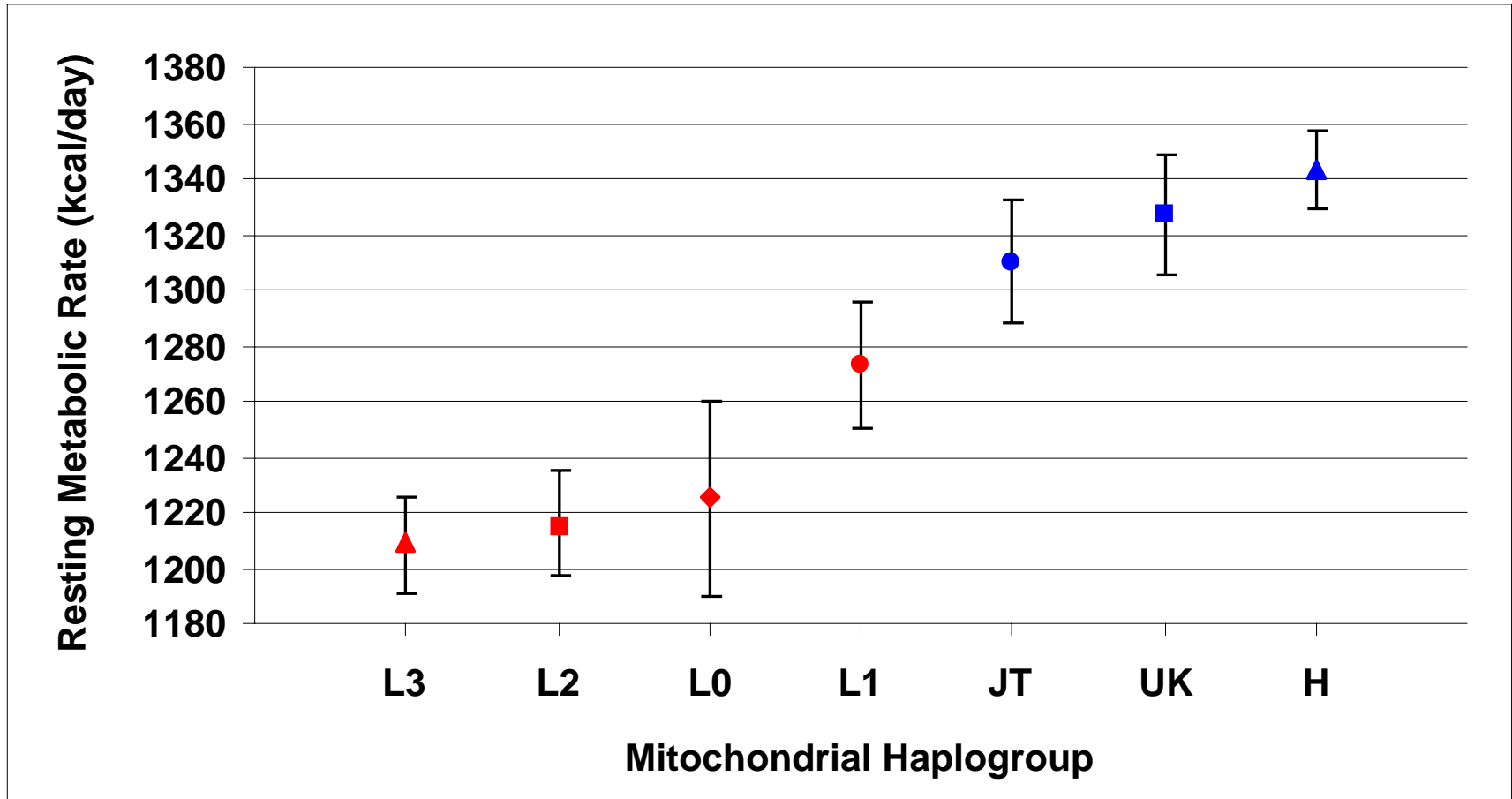
|                                     | <b>African</b>    | <b>European</b>  |                |
|-------------------------------------|-------------------|------------------|----------------|
| <b>Haplogroup</b>                   | <b>L</b>          | <b>N</b>         |                |
| <b>N</b>                            | <b>132</b>        | <b>162</b>       | <b>p-value</b> |
| <b>Age, years, mean (SD)</b>        | <b>73 (2.9)</b>   | <b>74 (2.8)</b>  | <b>0.12</b>    |
| <b>Sex</b>                          |                   |                  |                |
| <b>Female, n (%)</b>                | <b>64 (44)</b>    | <b>81 (56)</b>   | <b>0.29</b>    |
| <b>Male, n (%)</b>                  | <b>68 (46)</b>    | <b>64 (48)</b>   | <b>0.16</b>    |
| <b>Fat-free mass, kg, mean (SD)</b> | <b>48.7 (9.6)</b> | <b>46.6 (10)</b> | <b>0.07</b>    |

# Health, Aging and Body Composition Study

| Haplogroup                   | African    | European  |         |
|------------------------------|------------|-----------|---------|
| N                            | L          | N         | p-value |
| Age, years, mean (SD)        | 73 (2.9)   | 74 (2.8)  | 0.12    |
| Sex                          |            |           |         |
| Female, n (%)                | 64 (44)    | 81 (56)   | 0.29    |
| Male, n (%)                  | 68 (46)    | 64 (48)   | 0.16    |
| Fat-free mass, kg, mean (SD) | 48.7 (9.6) | 46.6 (10) | 0.07    |
| RMR kcal/d, Mean (SE)*       | 1221 (10)  | 1327 (9)  | <0.0001 |
| TEE kcal/d, Mean (SE)*       | 2073 (27)  | 2241 (25) | <0.0001 |

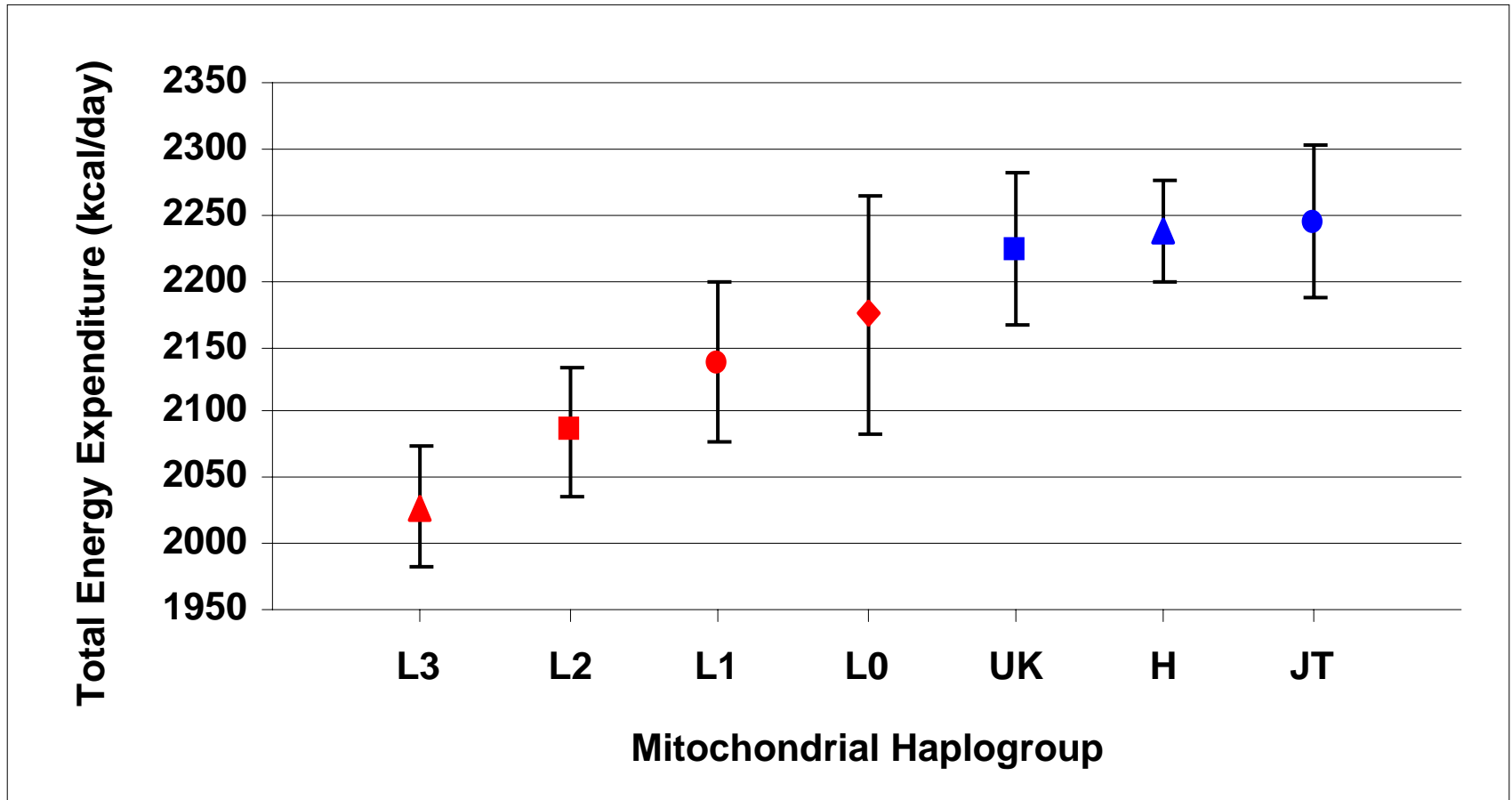
\* Values are Least Squares means and Standard Errors adjusted for age, sex, fat-free mass.

## Resting metabolic rate (kcal/day) for major mitochondrial haplogroups



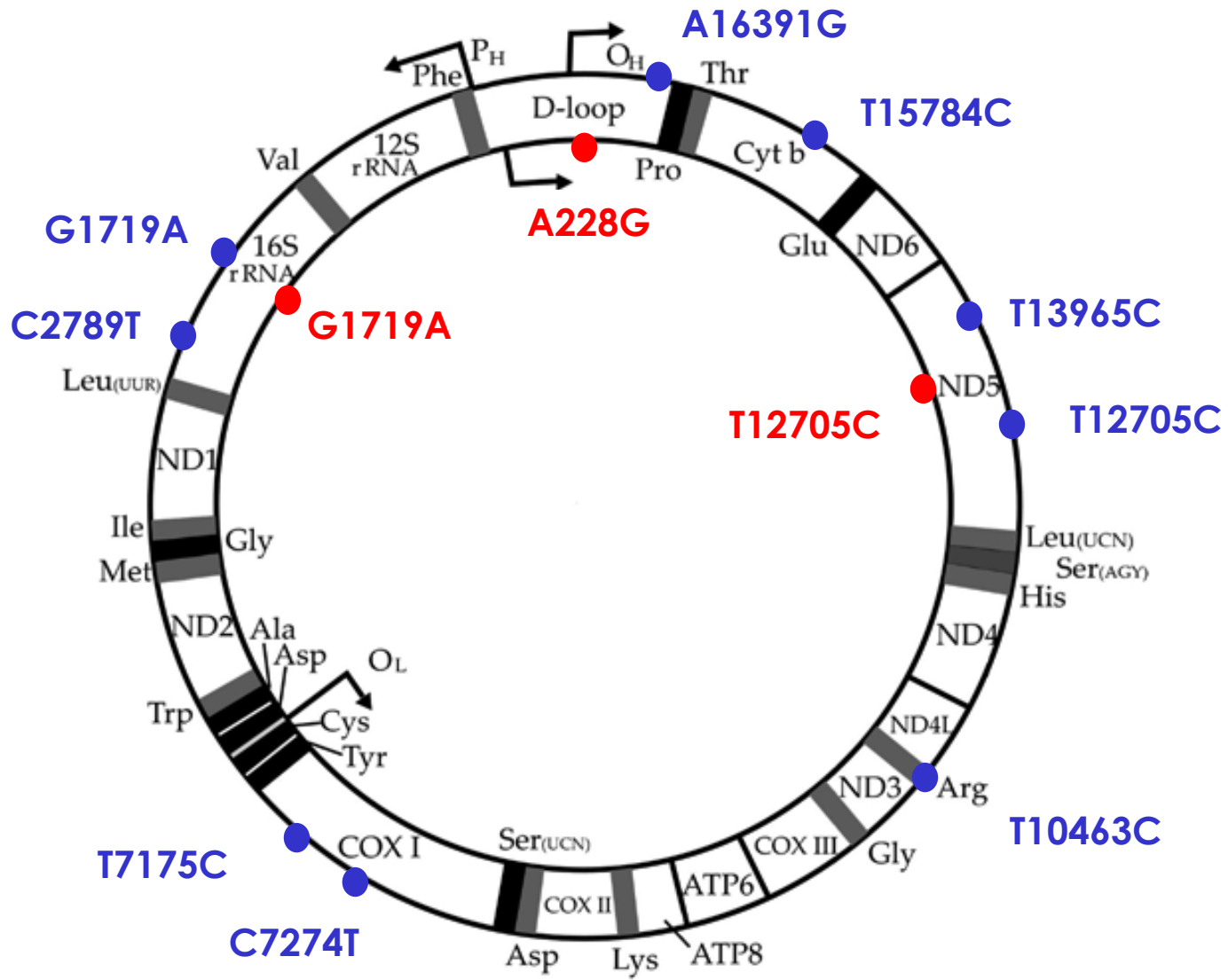
Values are LS means and SEs adjusted for age, sex, and fat-free mass

## Total energy expenditure (kcal/day) for major mitochondrial haplogroups



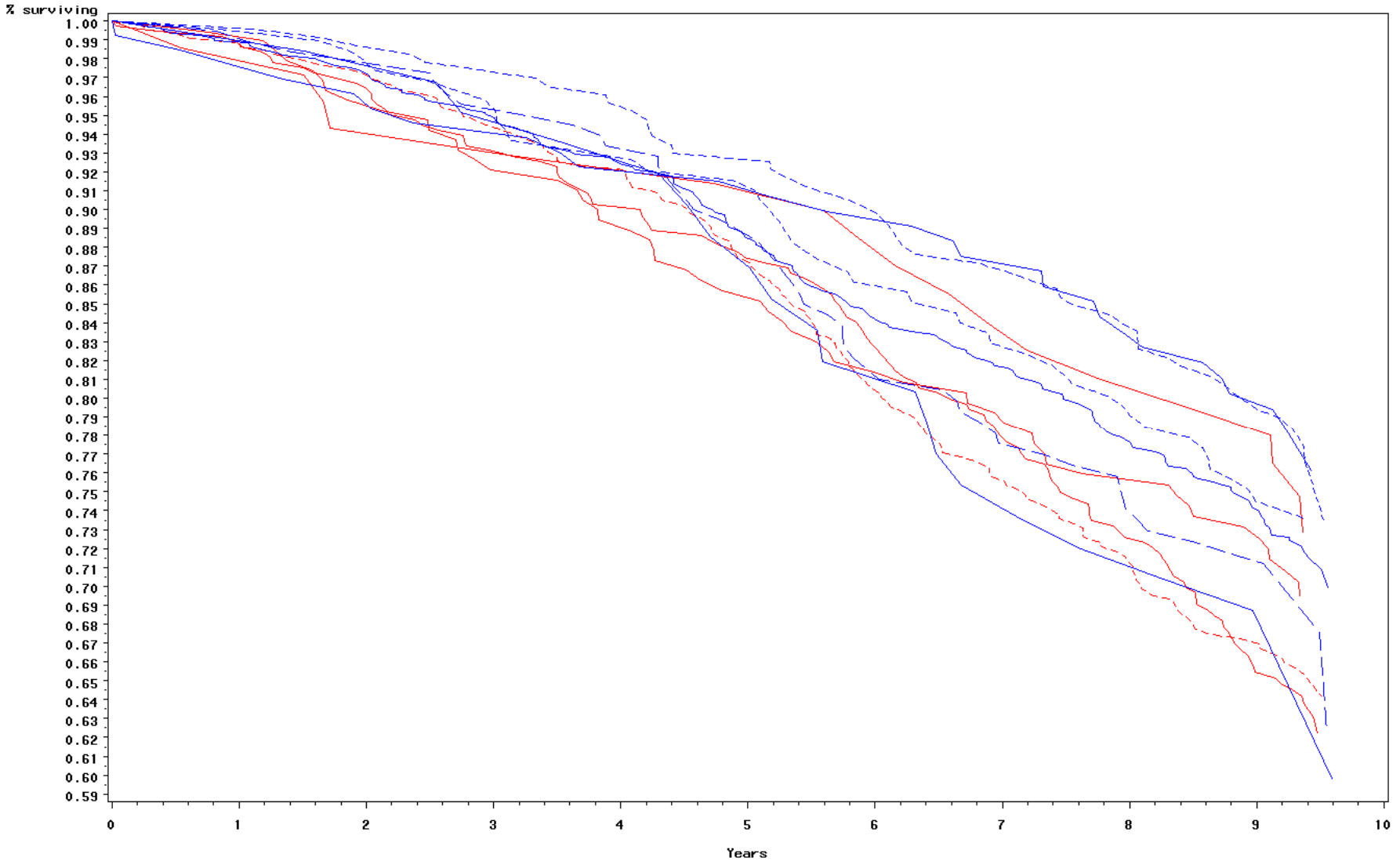
Values are LS means and SEs adjusted for age, sex, and fat-free mass

## Individual variants associated with RMR and TEE



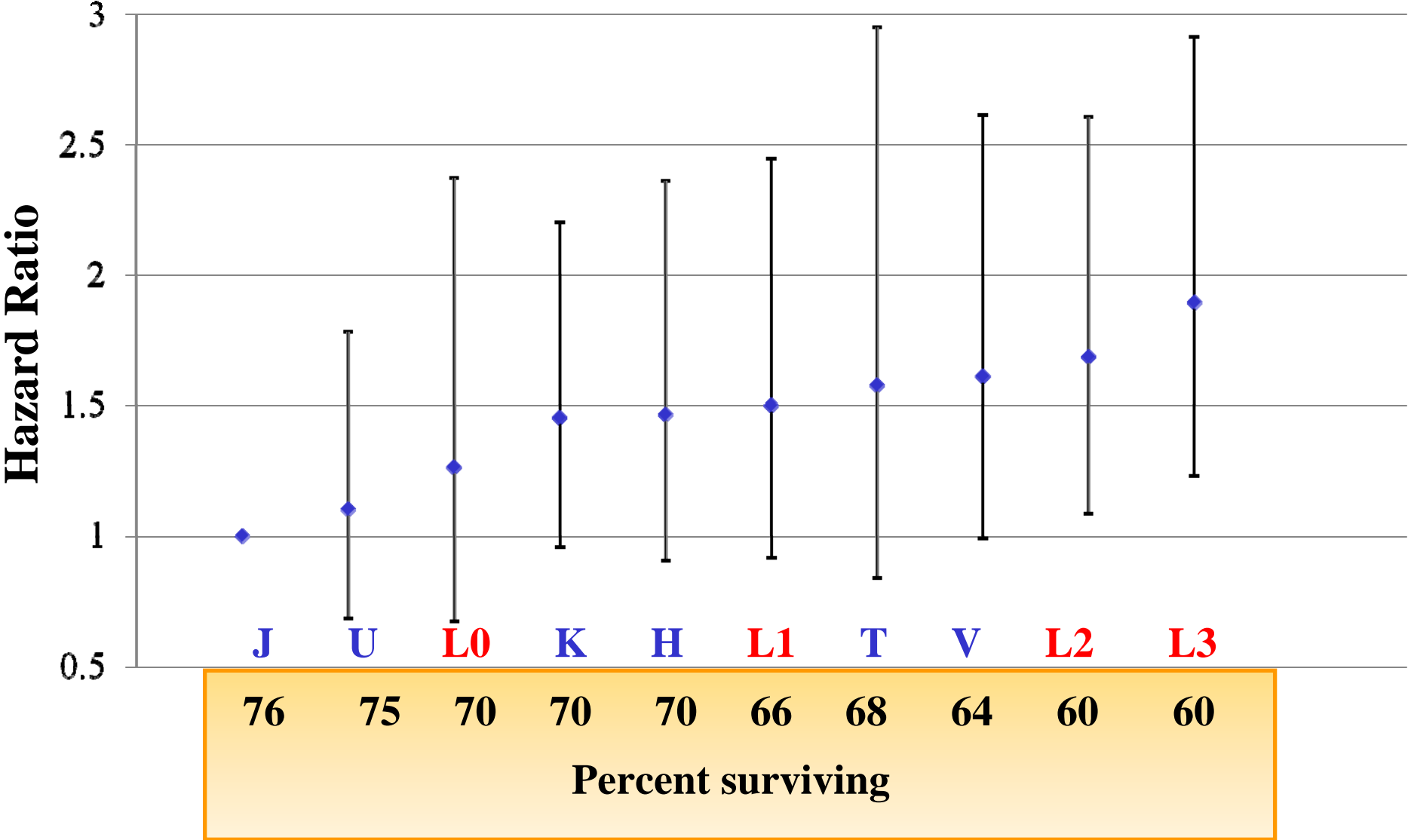
Adjusted for age, sex, fat-free mass and 6 eigenvectors of mitochondrial genetic ancestry.

# 10 year mortality



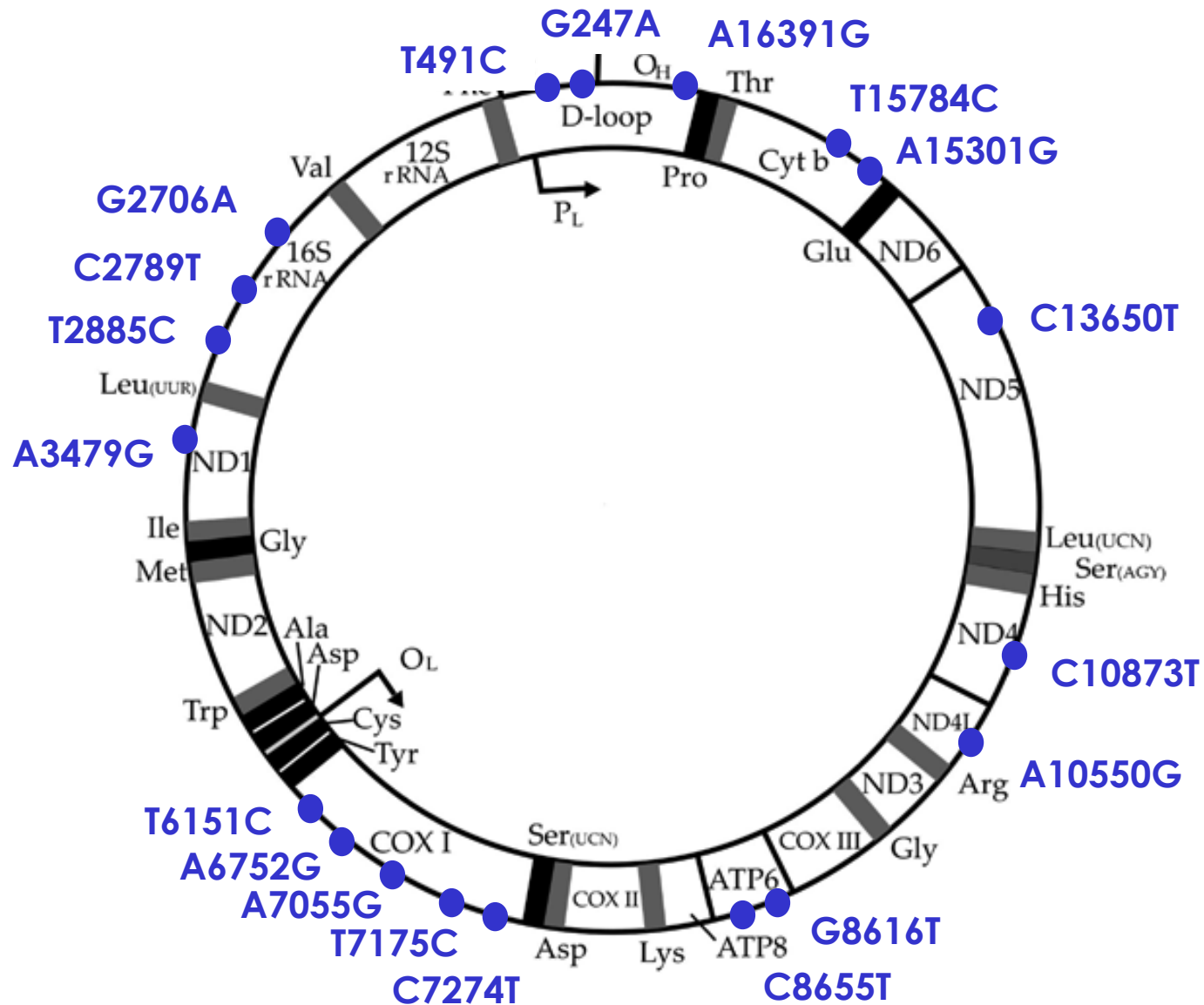
Kaplan-Meier survival curves showing the cumulative incidence of all-cause mortality. Adjusted for sex, education and income.

# Health ABC 10 Year Mortality



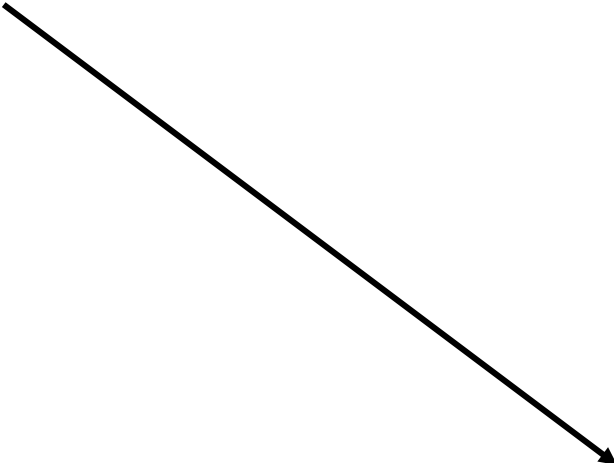
Age at death adjusted for sex, education and income.

## Individual variants associated with Mortality

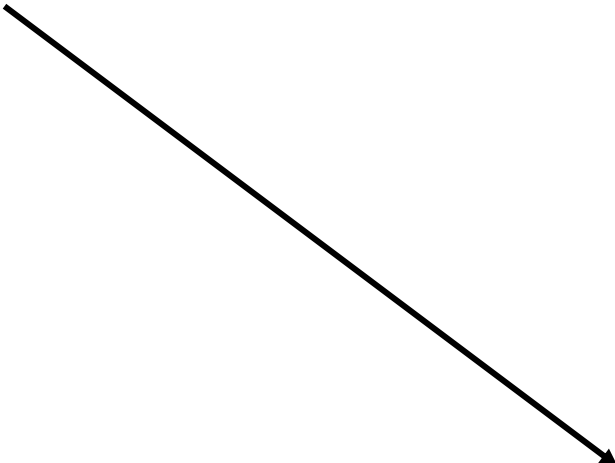


Adjusted for sex, education, income and 6 eigenvectors of mitochondrial genetic ancestry.

**mtDNA**

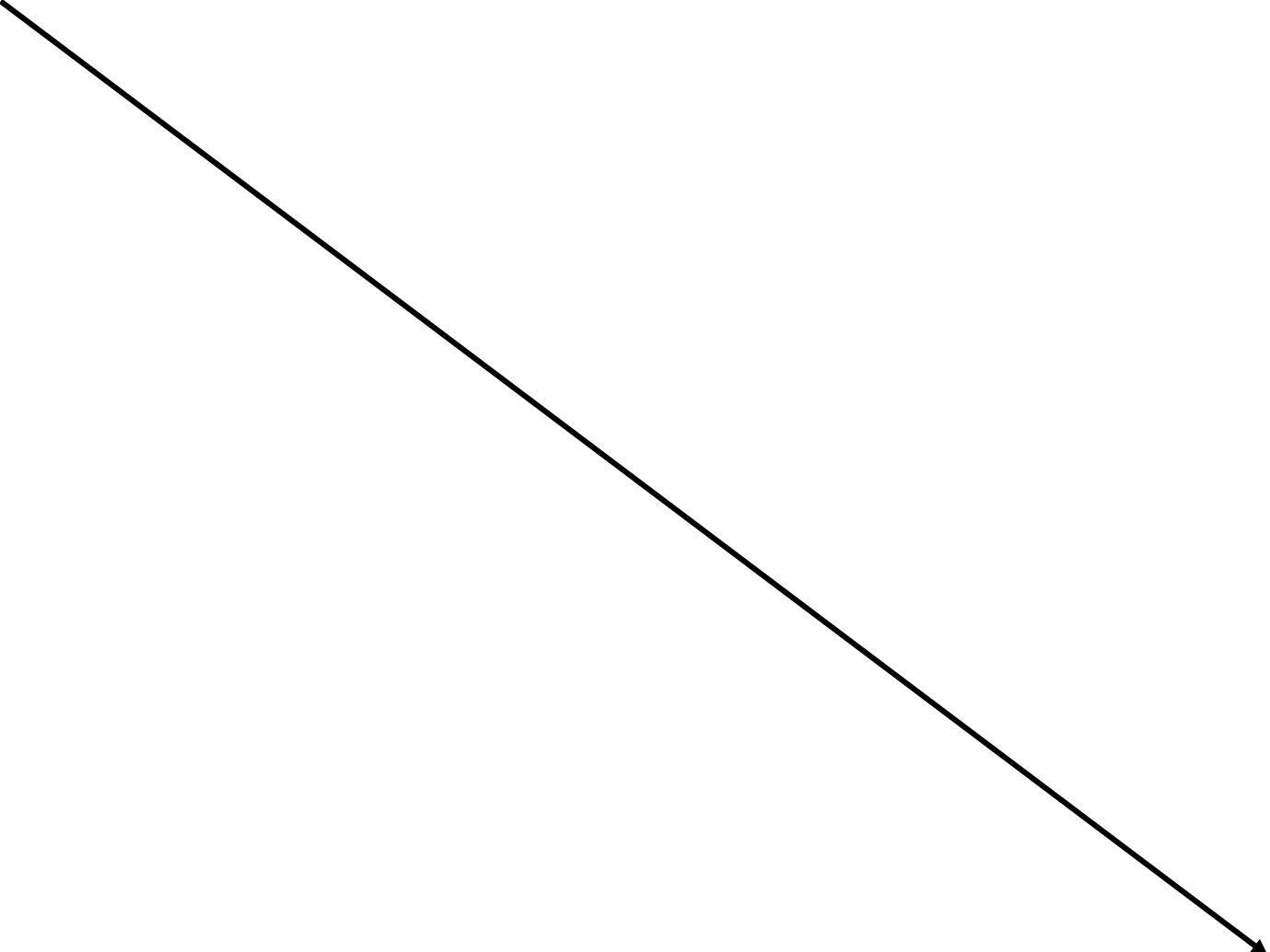


**Energetics**



**Mortality**

**mtDNA**



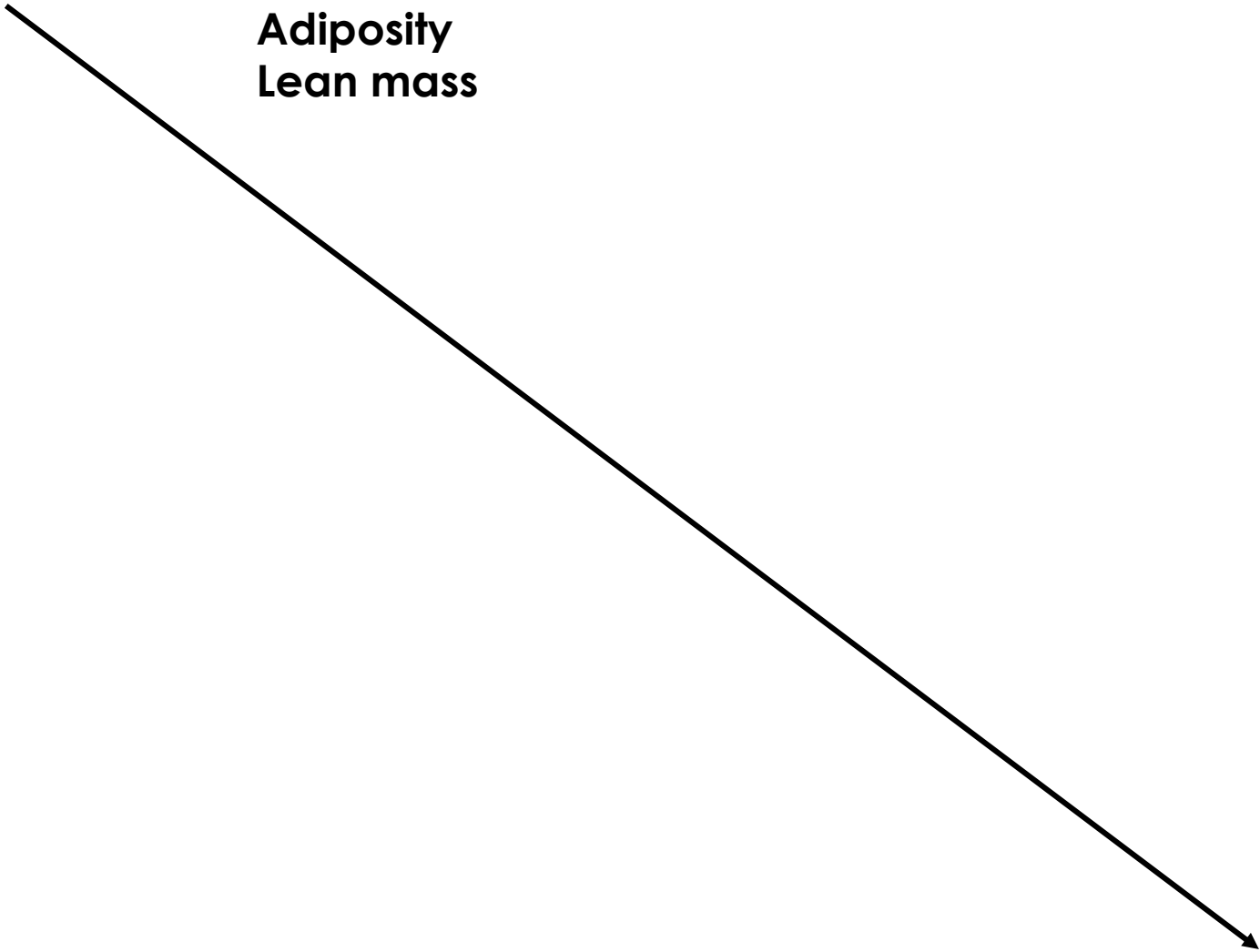
**Mortality**

**mtDNA**

**Body Composition**

**Adiposity**

**Lean mass**



**Mortality**

**mtDNA**

**Body Composition**

**Adiposity**

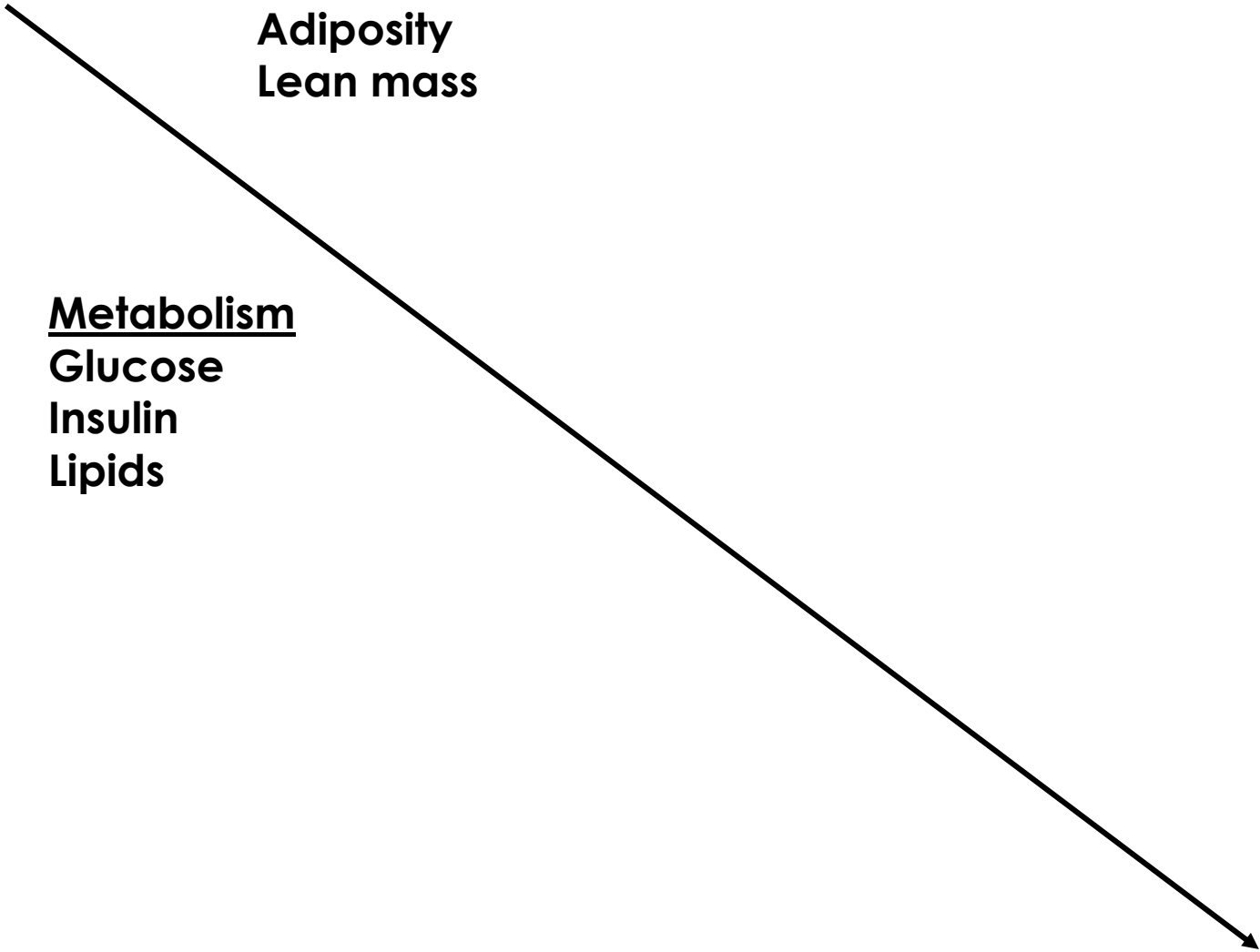
**Lean mass**

**Metabolism**

**Glucose**

**Insulin**

**Lipids**



**Mortality**

**mtDNA**

**Body Composition**

**Adiposity**

**Lean mass**

**Metabolism**

**Glucose**

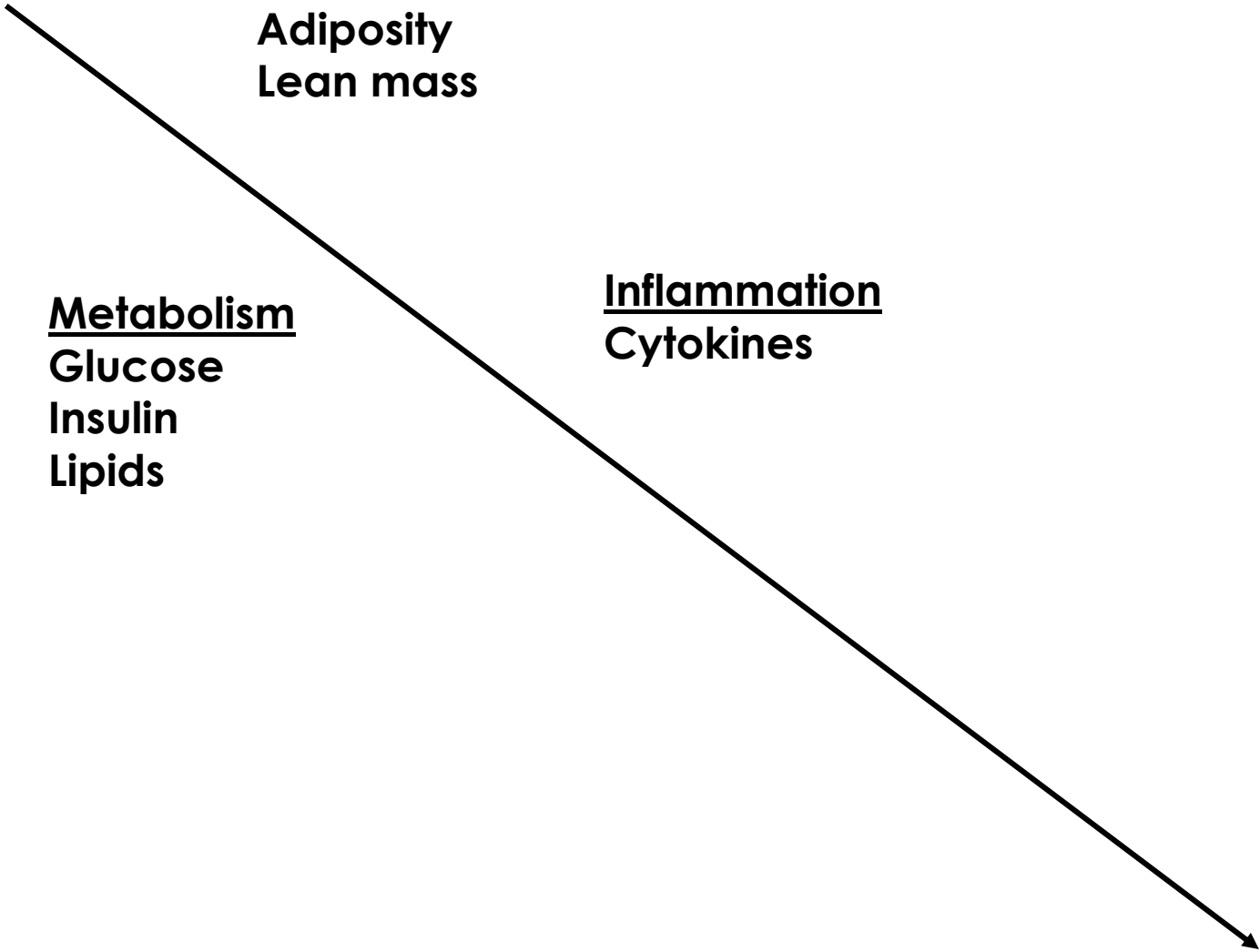
**Insulin**

**Lipids**

**Inflammation**

**Cytokines**

**Mortality**



**mtDNA**

Body Composition

Adiposity

Lean mass

Metabolism

Glucose

Insulin

Lipids

Inflammation

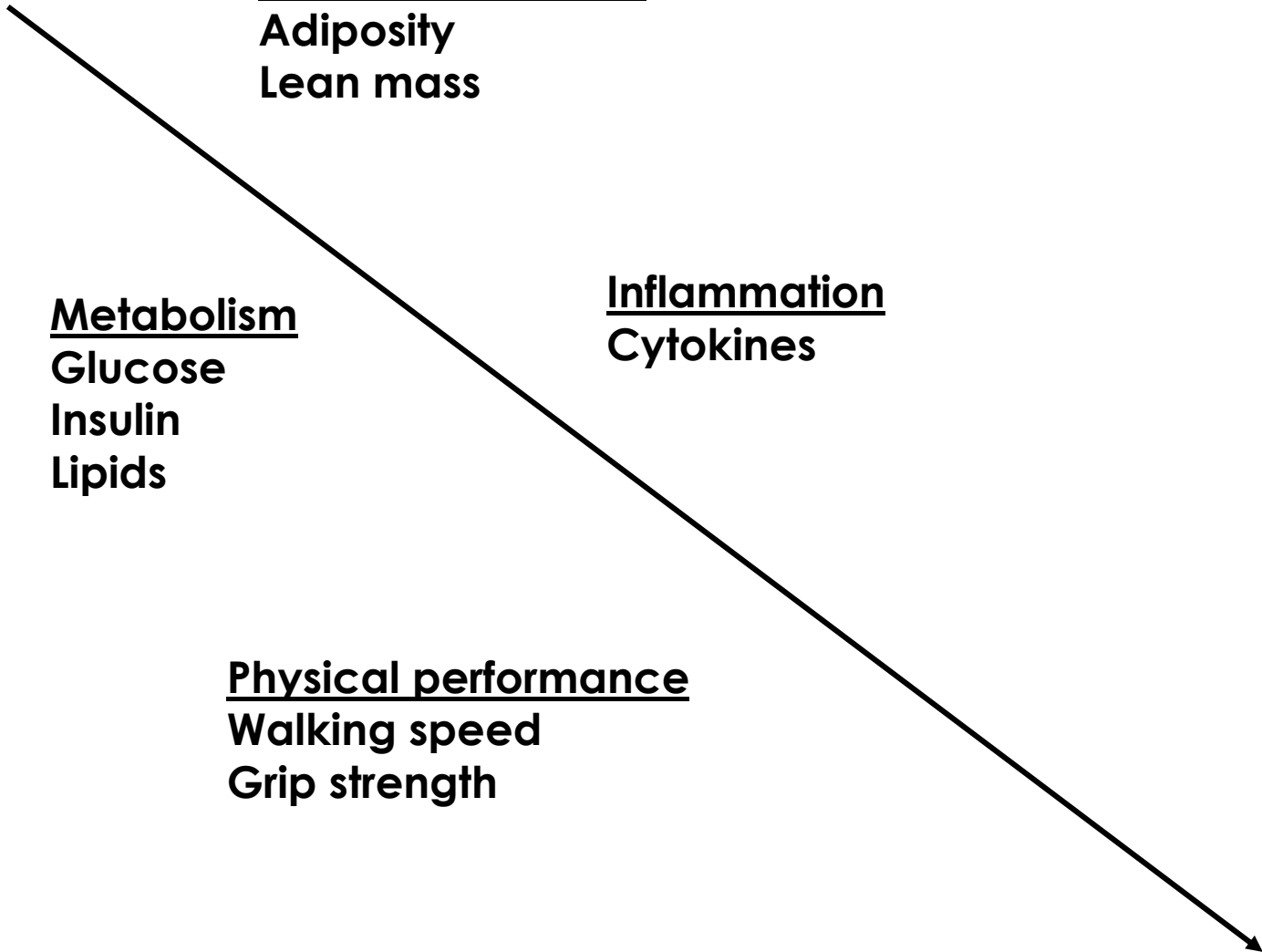
Cytokines

Physical performance

Walking speed

Grip strength

**Mortality**



**mtDNA**

**Body Composition**

**Adiposity**  
**Lean mass**

**Metabolism**

**Glucose**  
**Insulin**  
**Lipids**

**Inflammation**

**Cytokines**

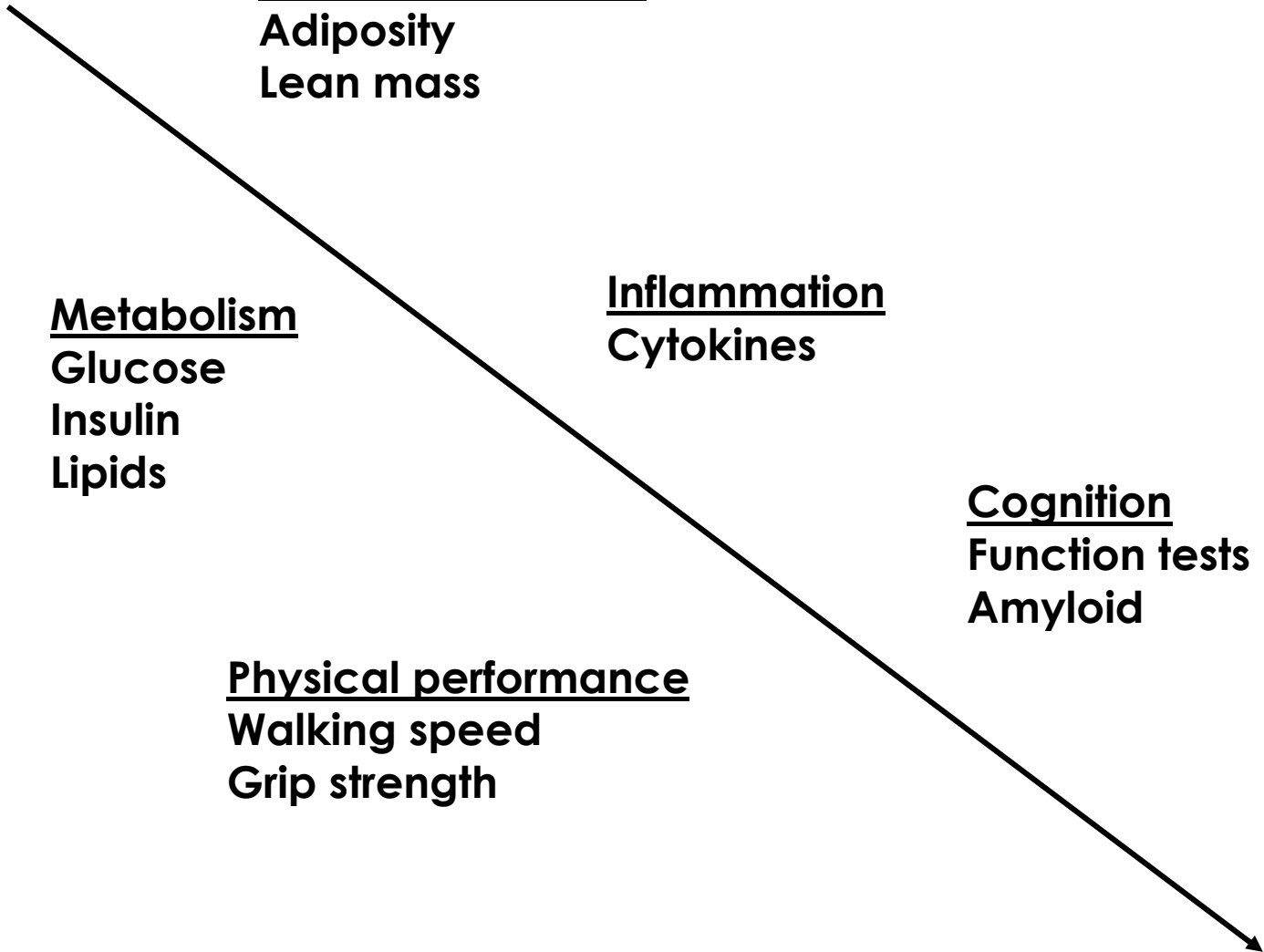
**Cognition**

**Function tests**  
**Amyloid**

**Physical performance**

**Walking speed**  
**Grip strength**

**Mortality**



**mtDNA**

Body Composition

Adiposity  
Lean mass

Metabolism

Glucose  
Insulin  
Lipids

Inflammation

Cytokines

Cognition

Function tests  
Amyloid

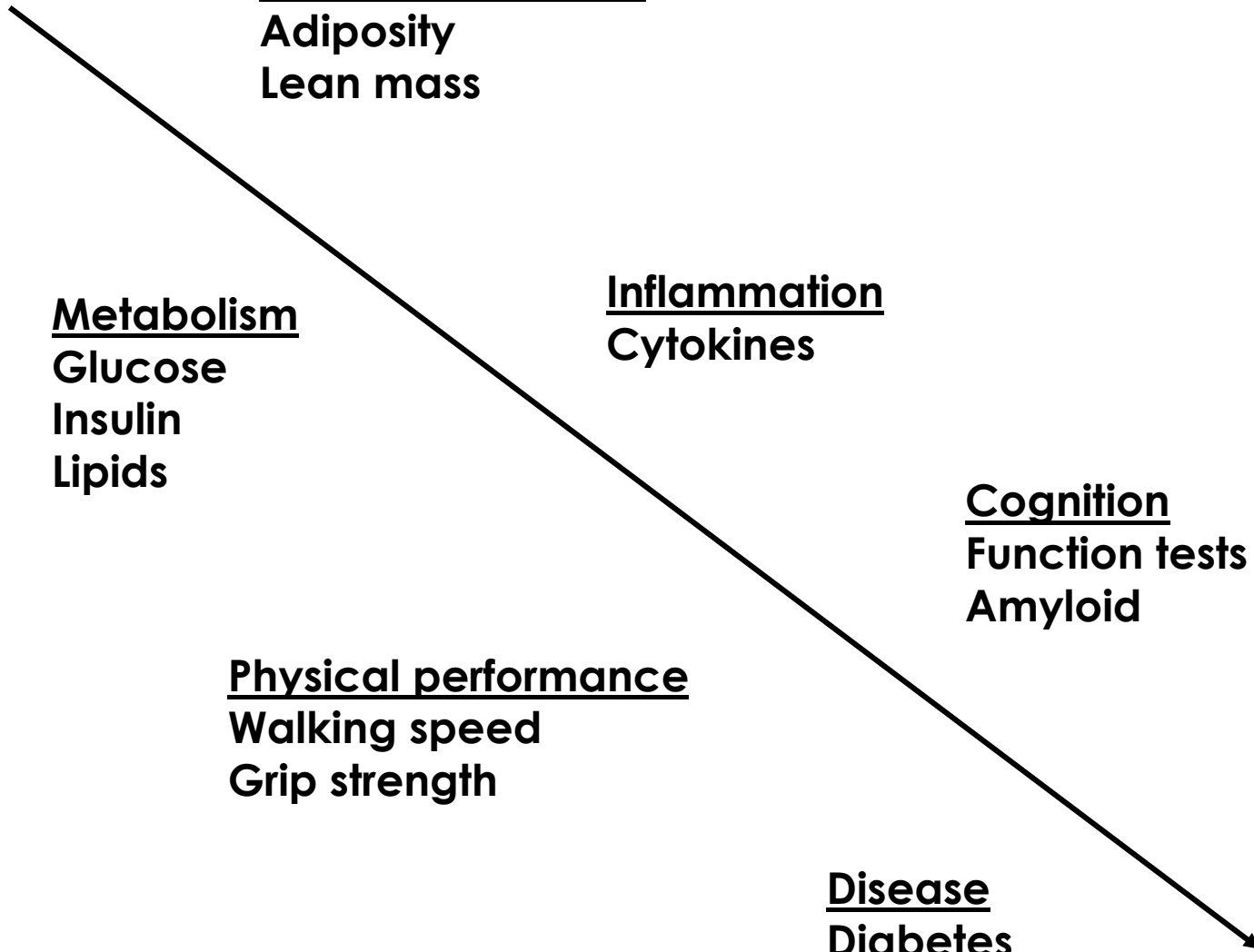
Physical performance

Walking speed  
Grip strength

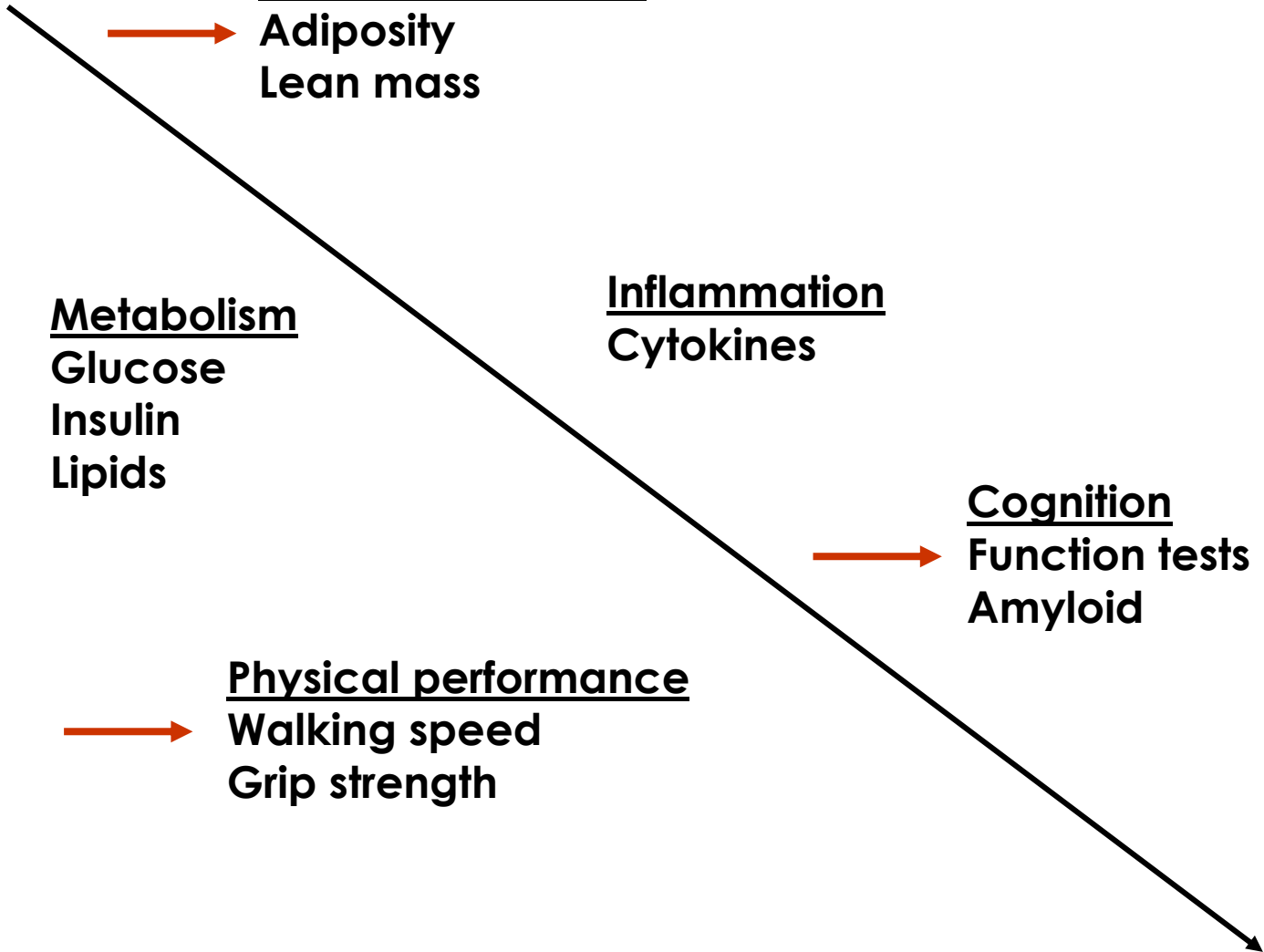
Disease

Diabetes  
Cancer  
Heart disease

**Mortality**



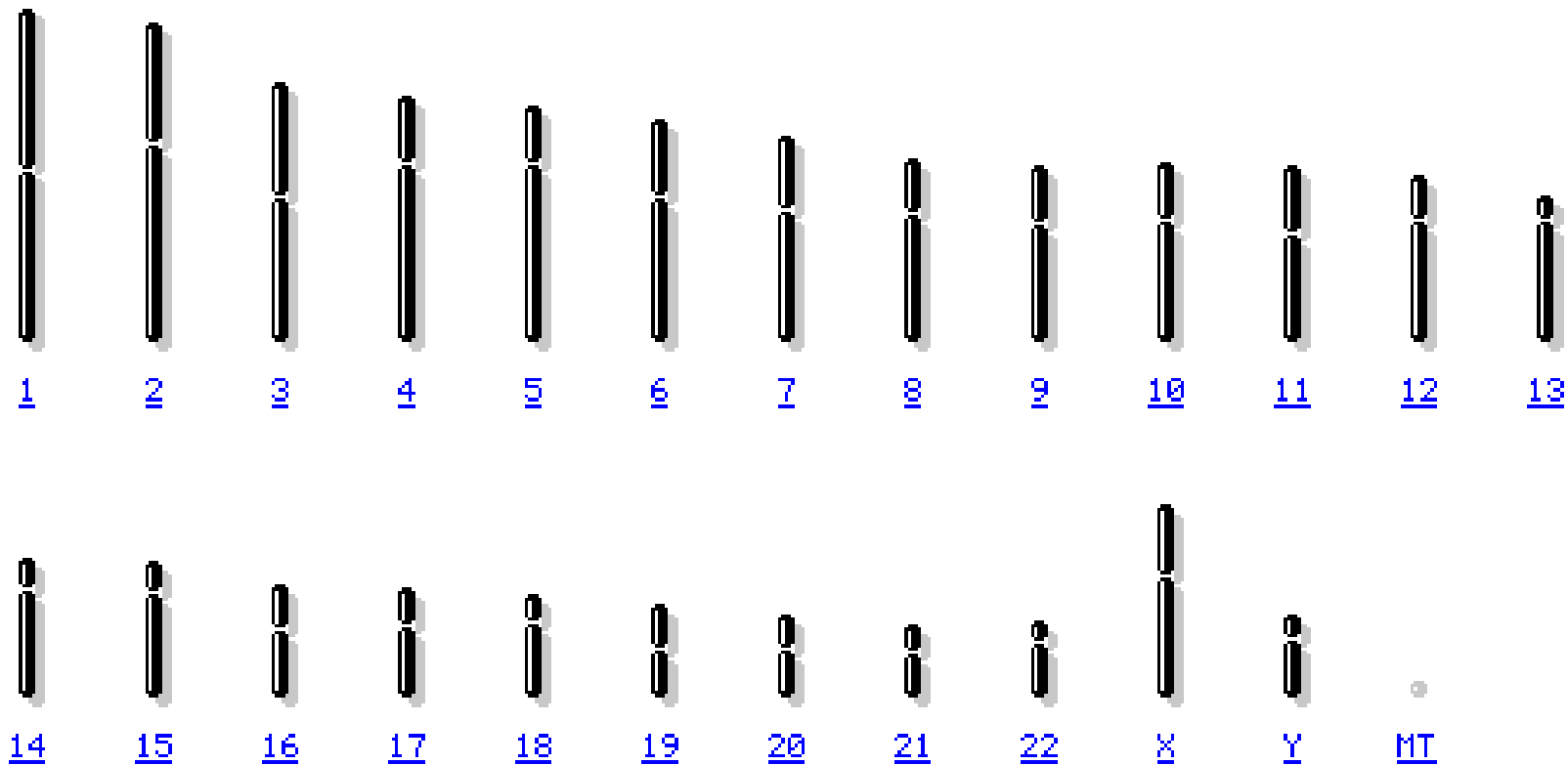
**mtDNA**

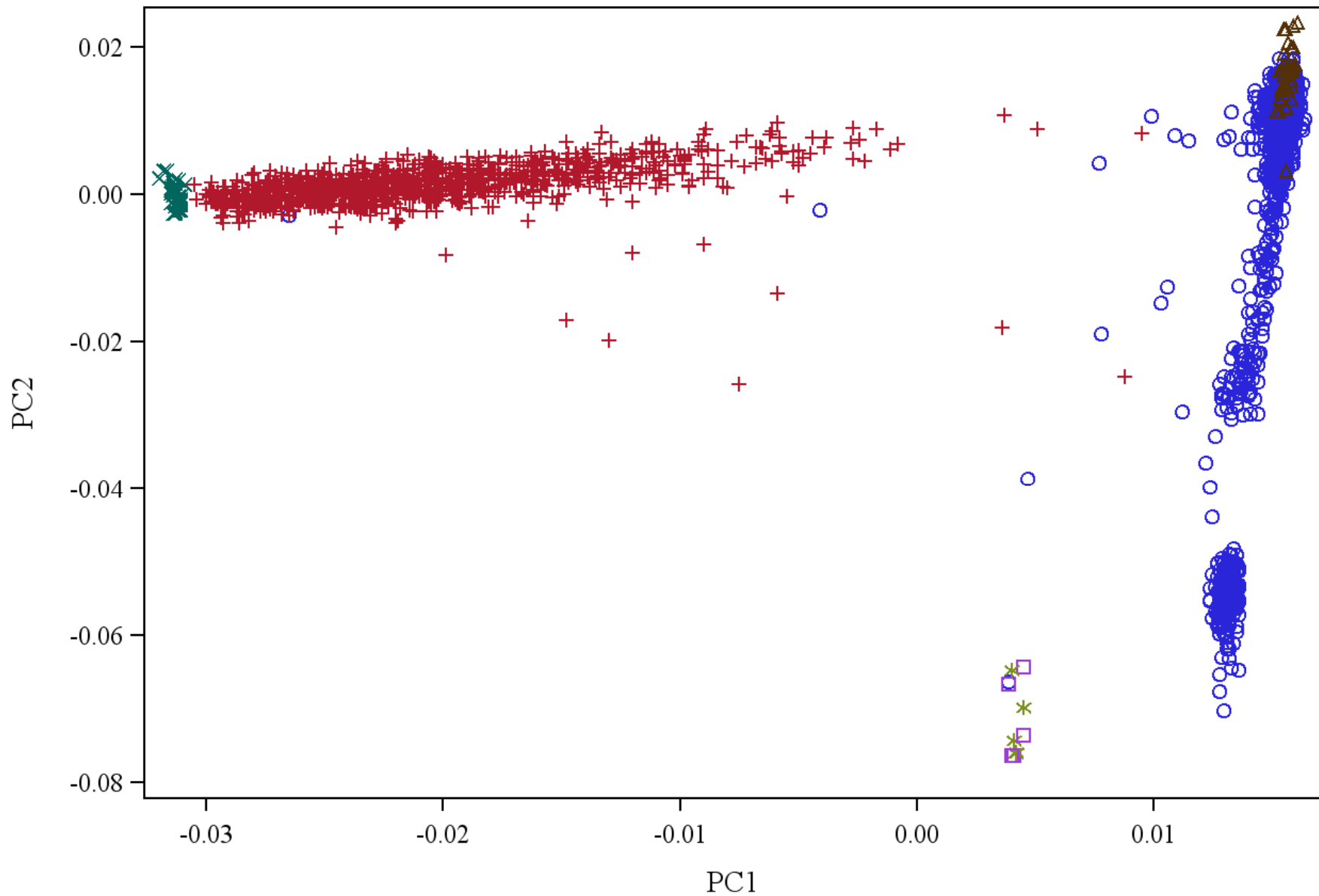


**Mortality**

# Homo sapiens (human) genome view

[Build 37.1 statistics](#) [Switch to previous build](#)

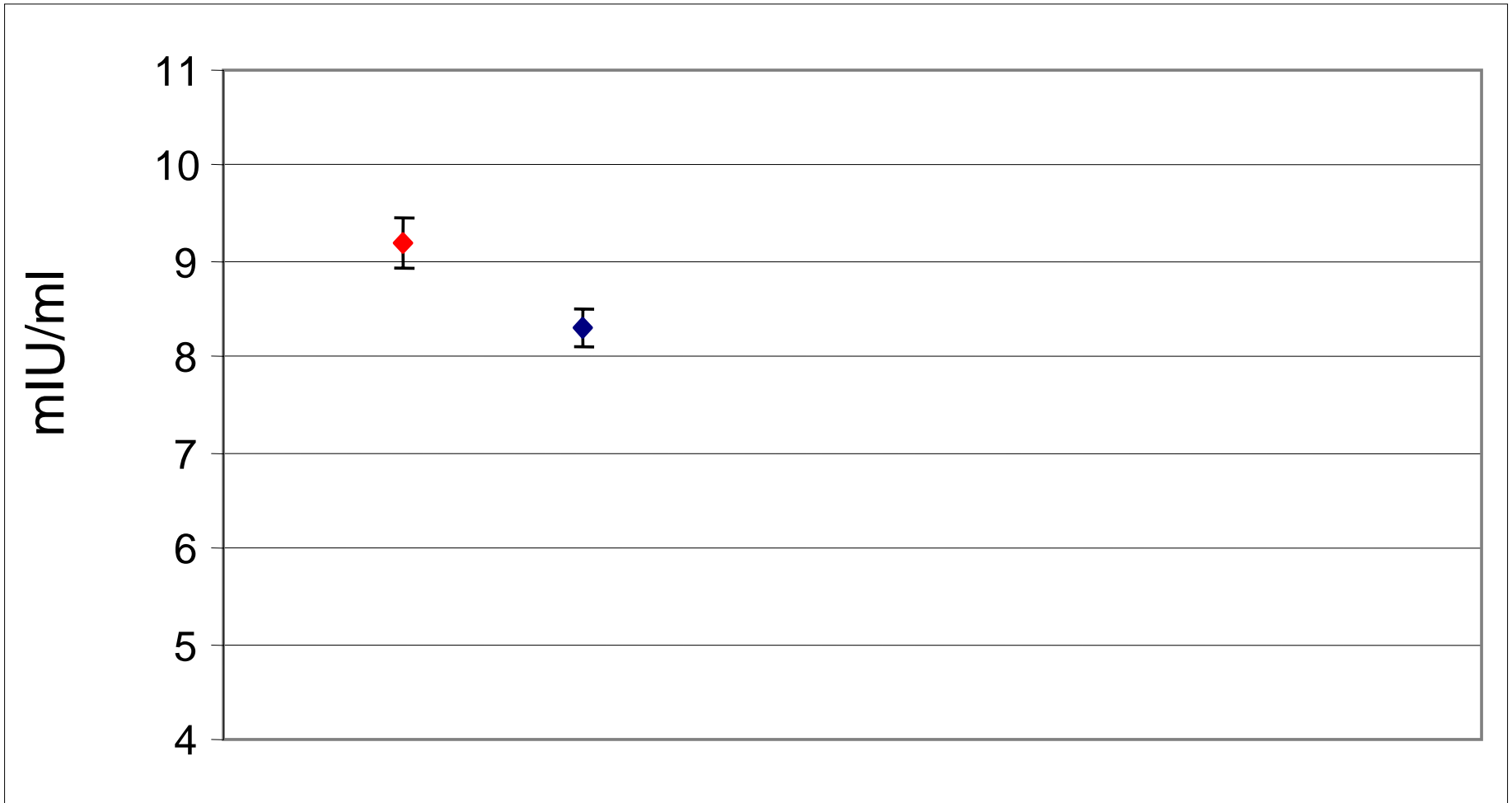




Race groups with all hapmap sources separate

|         |         |         |        |         |         |
|---------|---------|---------|--------|---------|---------|
| ○ White | + Black | × YORUB | △ CEPH | □ HAN C | * JAPAN |
|---------|---------|---------|--------|---------|---------|

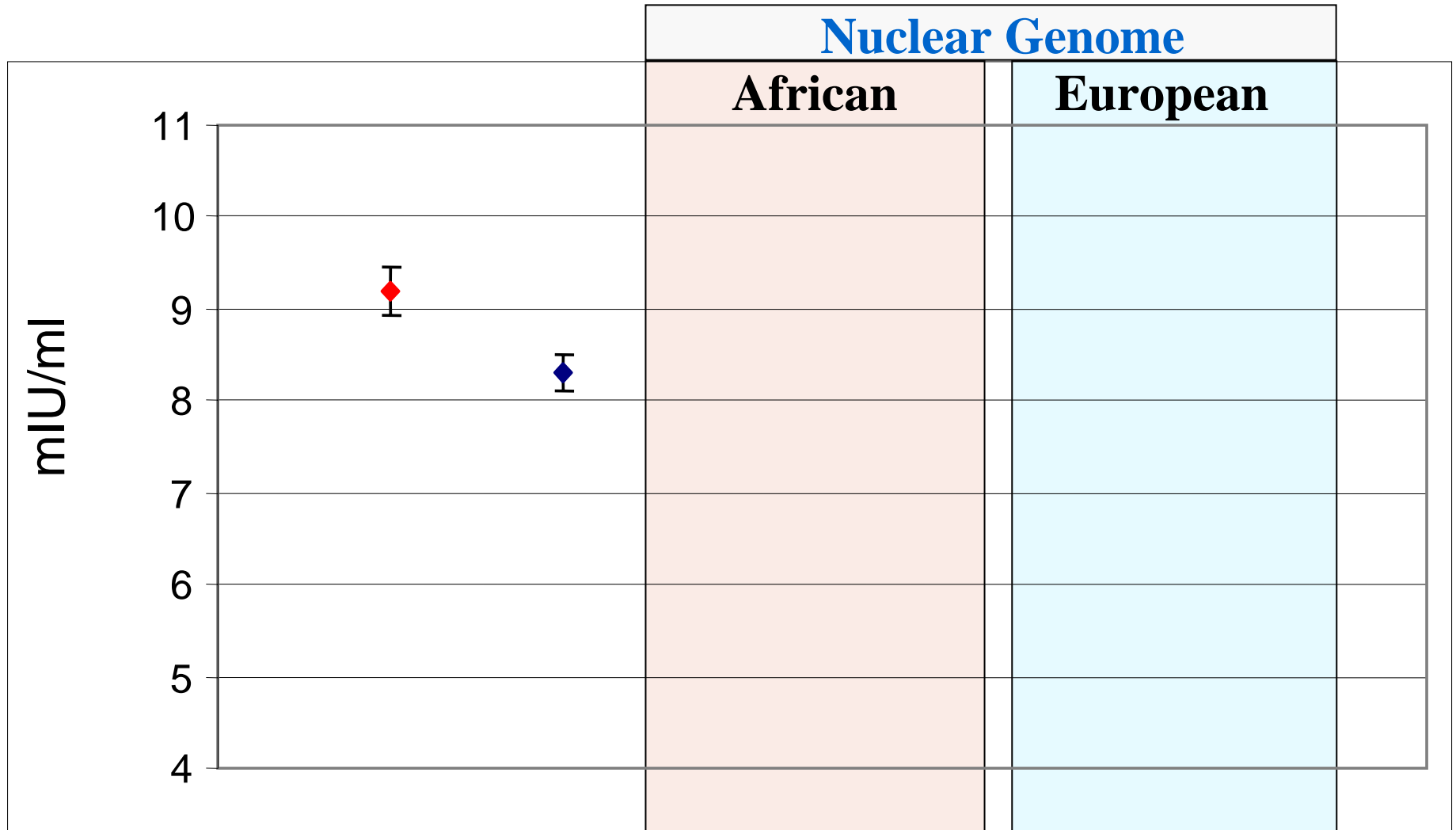
# Fasting Insulin (mIU/mL)



**L**      **N**  
**(1058)**   **(1706)**

**Values are LS means and SEs adjusted for age and sex**

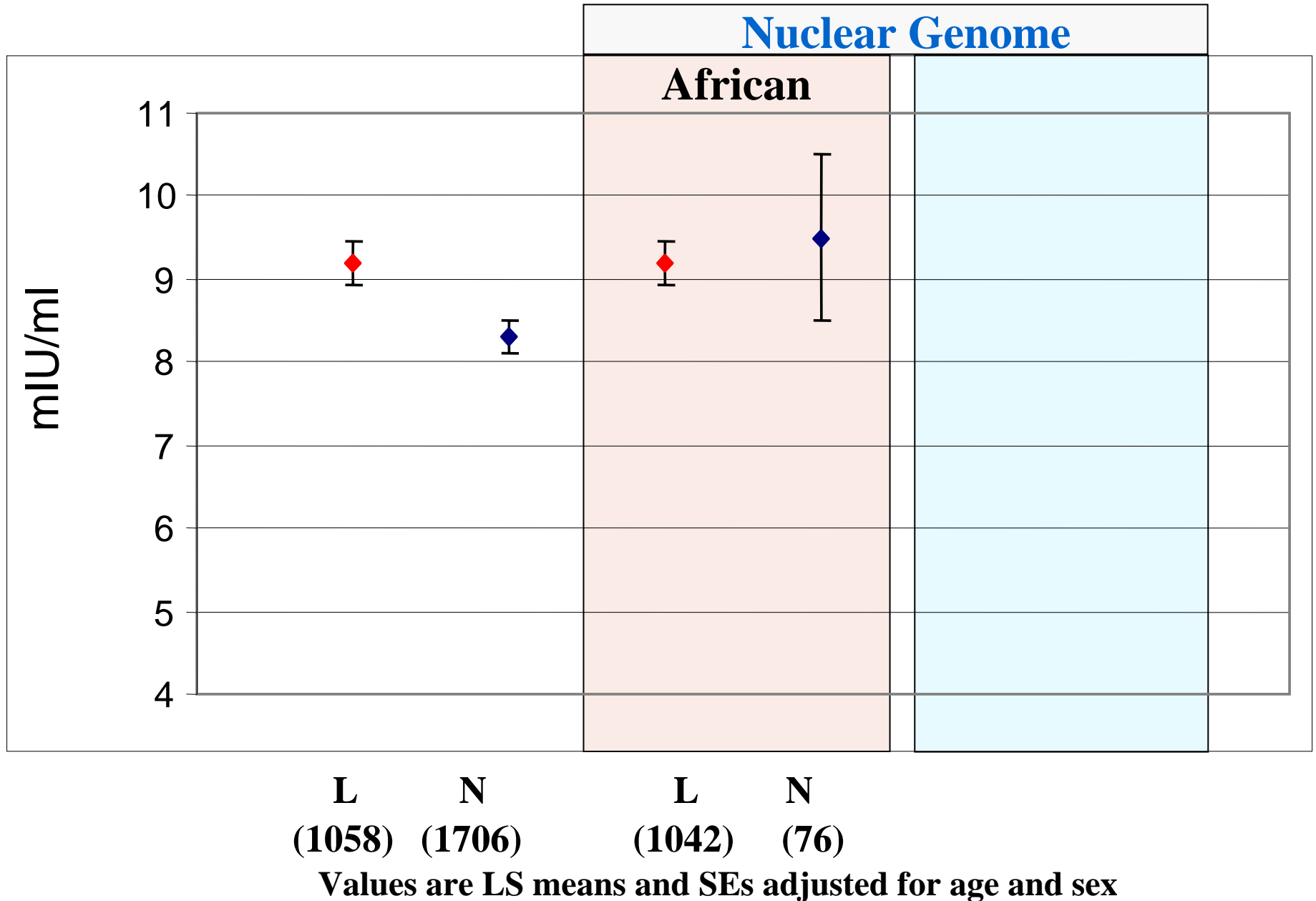
# Fasting Insulin (mIU/mL)



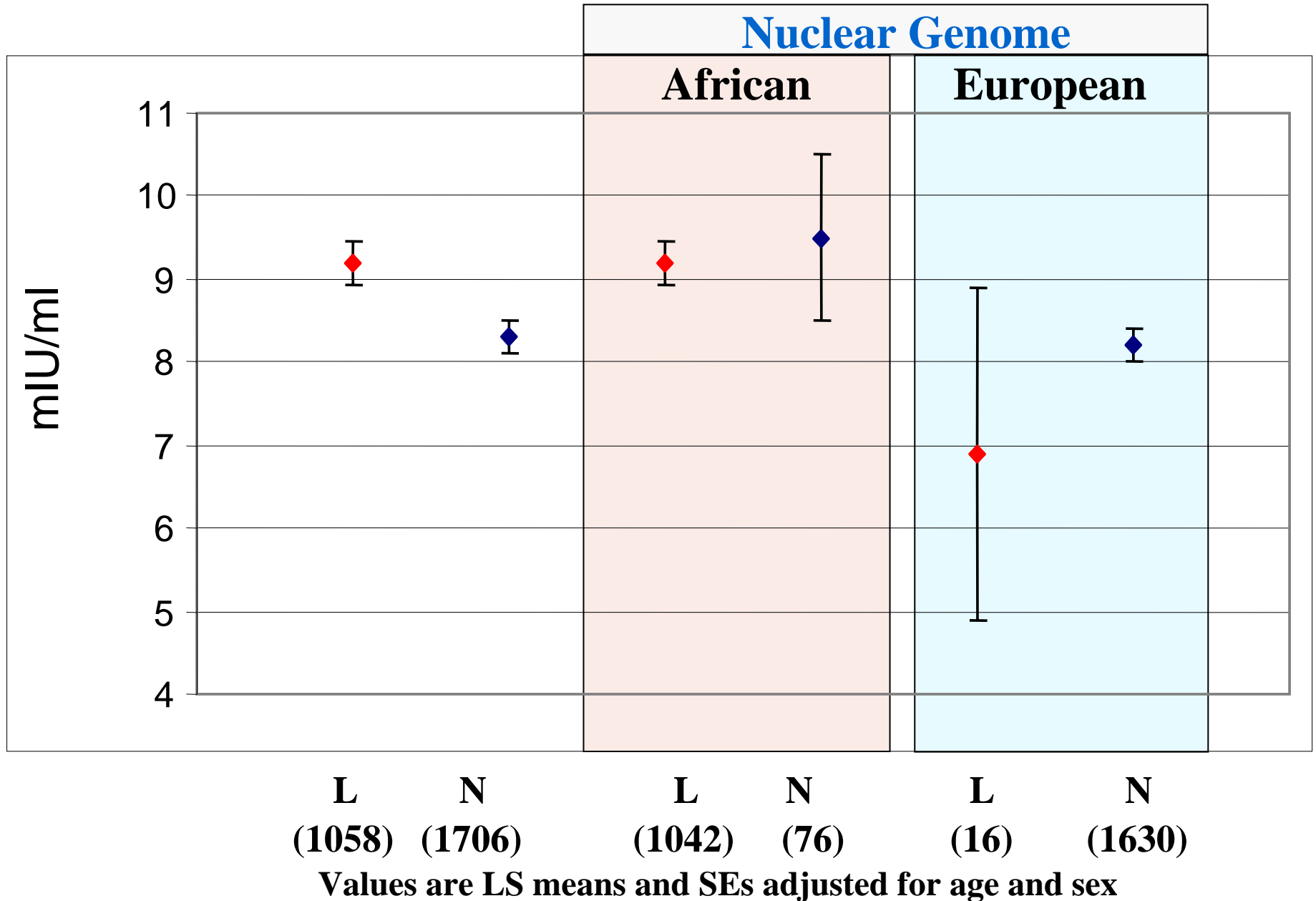
**L**      **N**  
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# Fasting Insulin (mIU/mL)

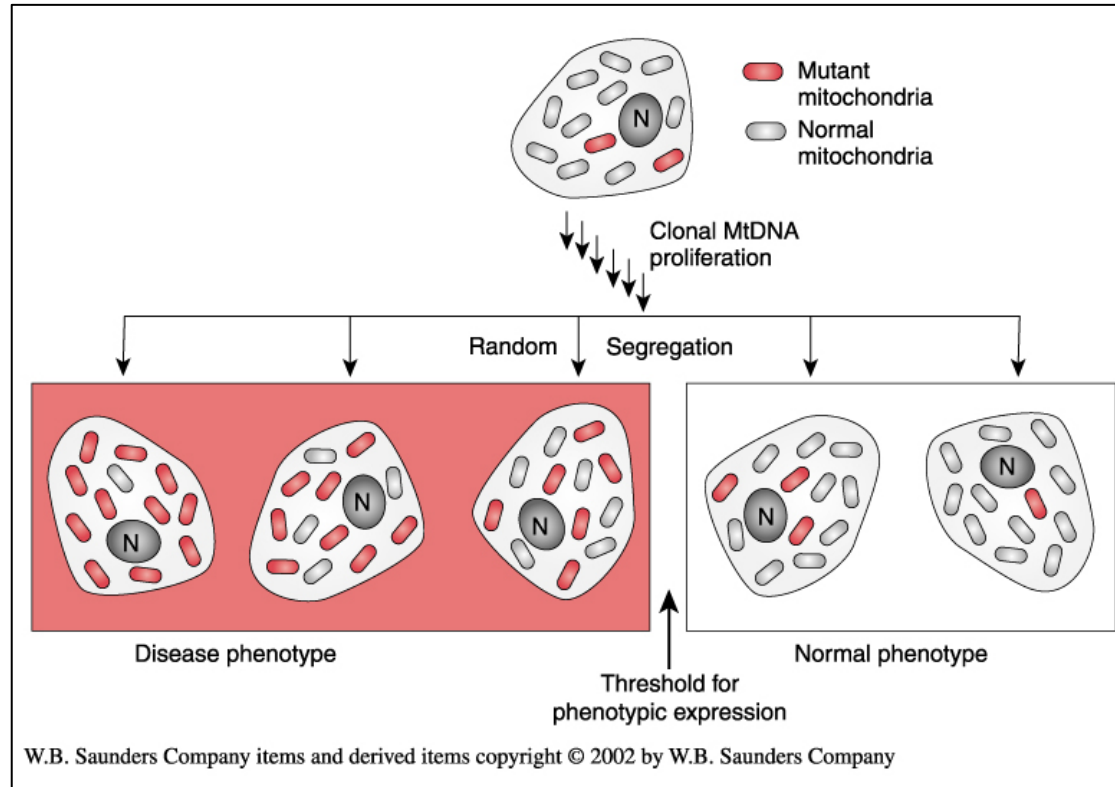


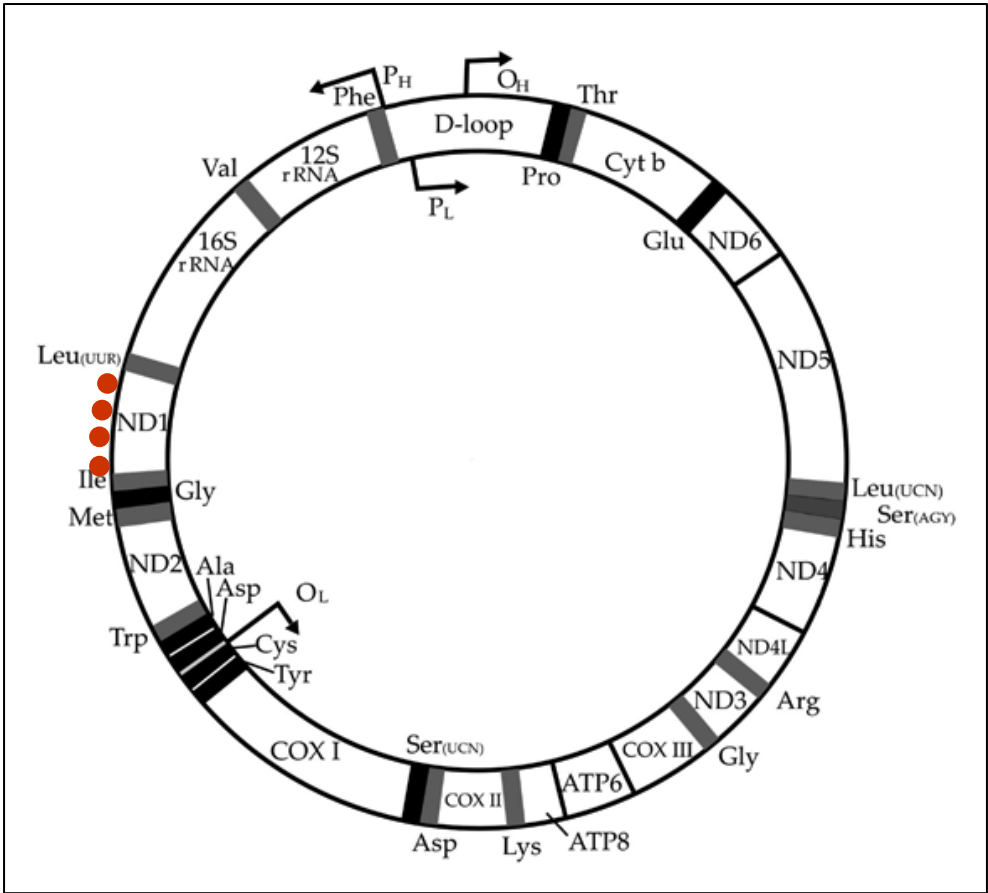
# Fasting Insulin (mIU/mL)



# Heteroplasmy

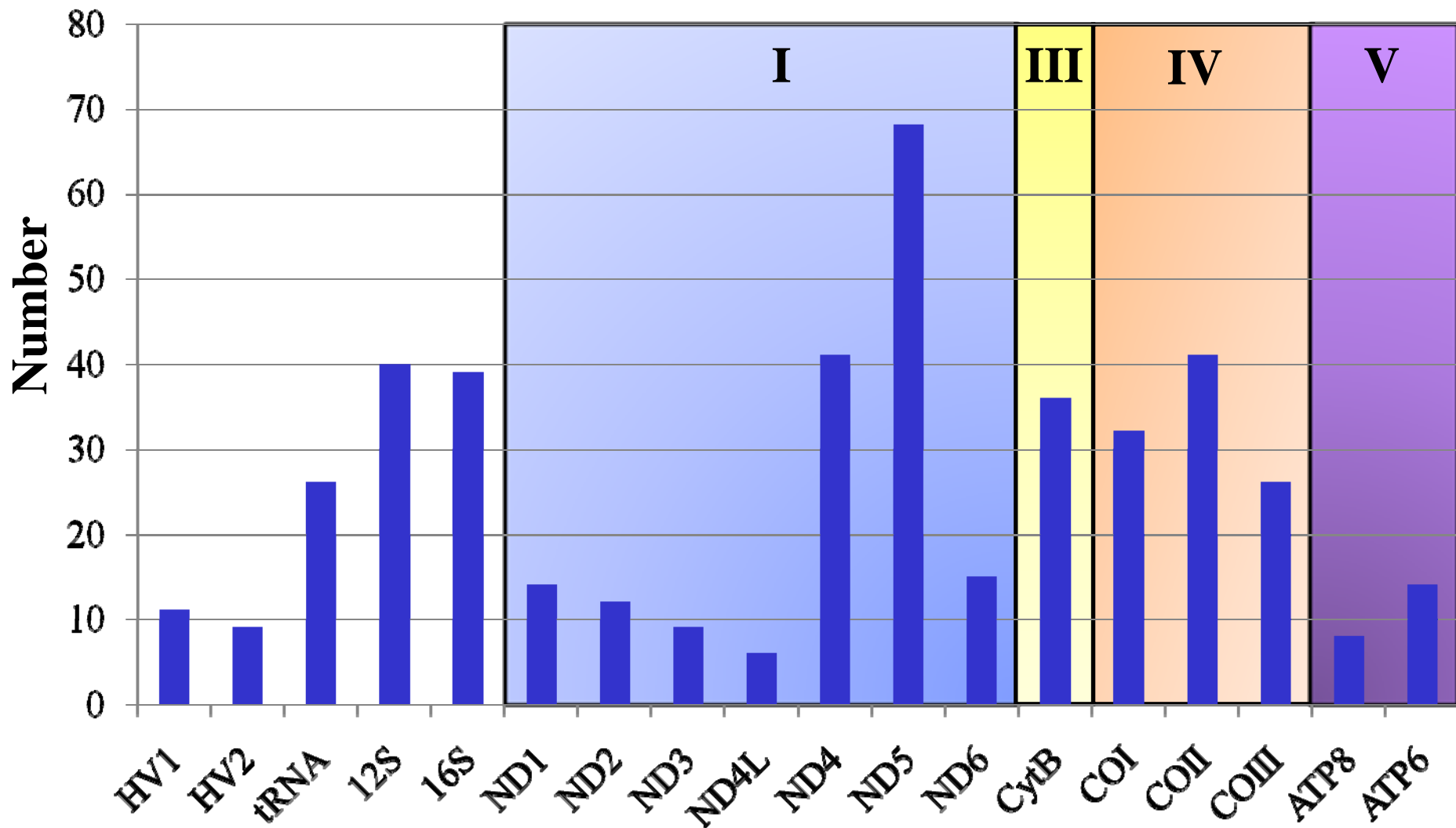
A heterogeneous population of normal and mutant mtDNA molecules in the cell.





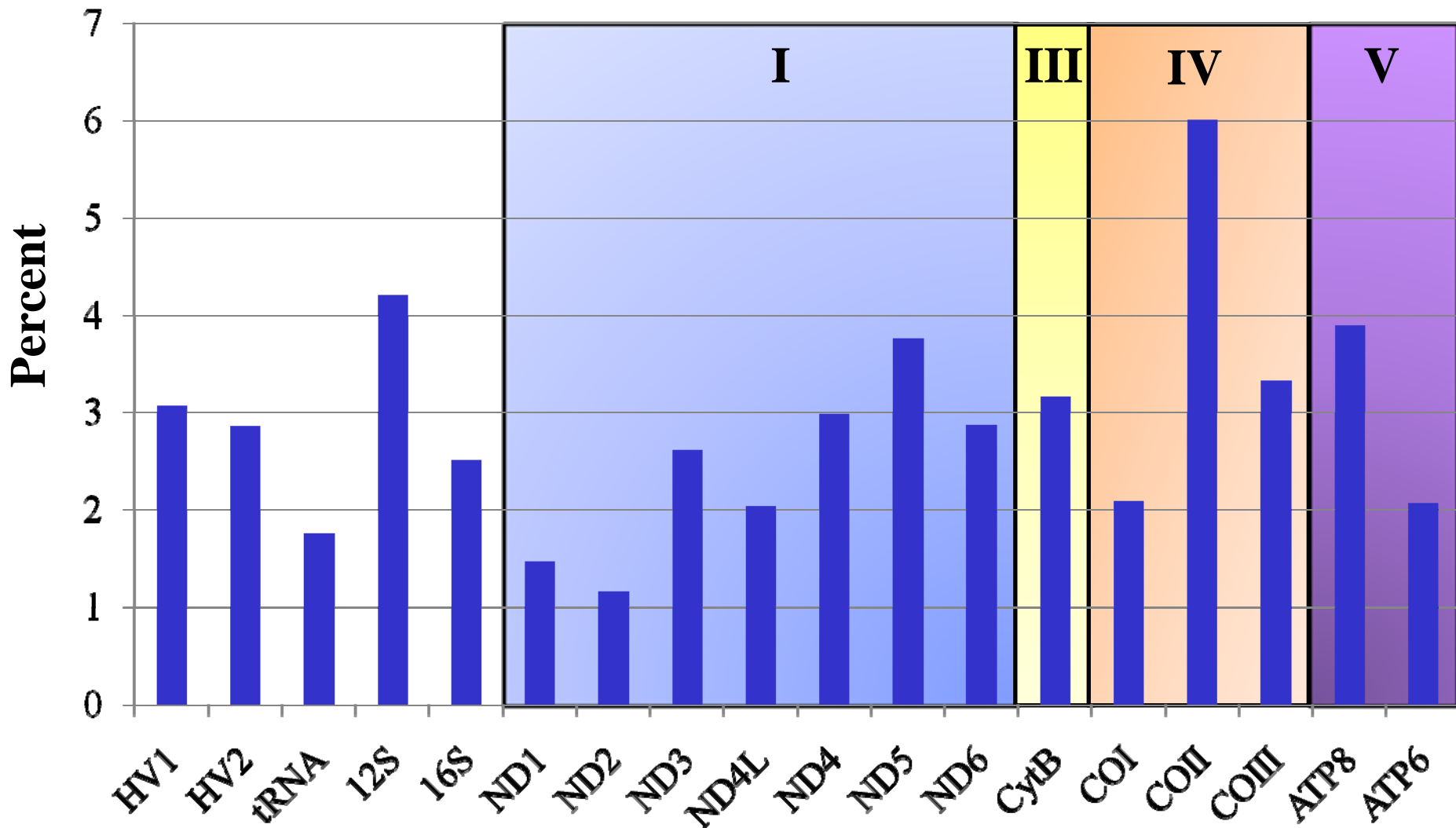


## Resting Metabolic Rate (n=138)



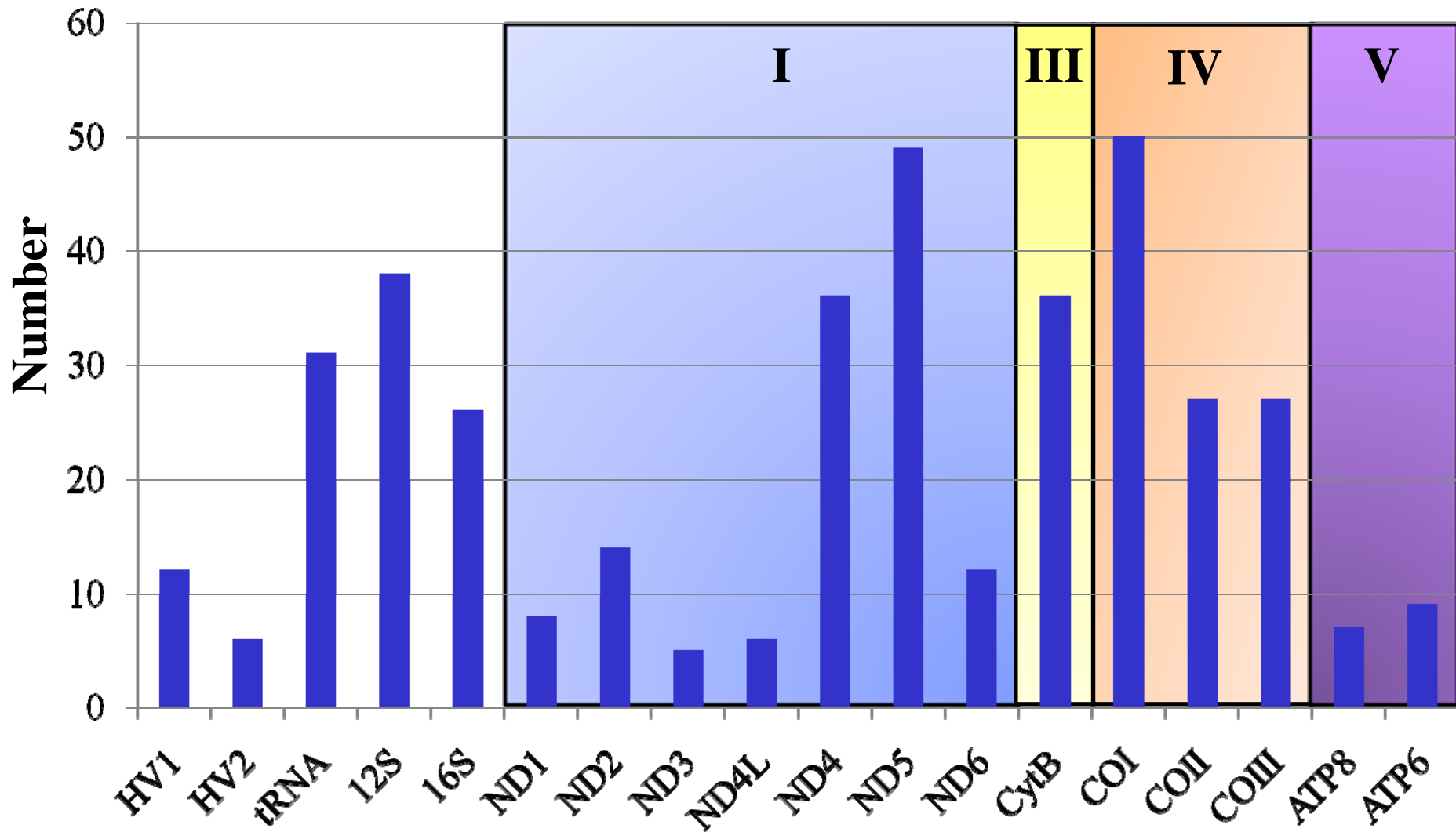
Number of mtDNA heteroplasmic sites associated with RMR ( $p < 0.05$ )

## Resting Metabolic Rate (n=138)



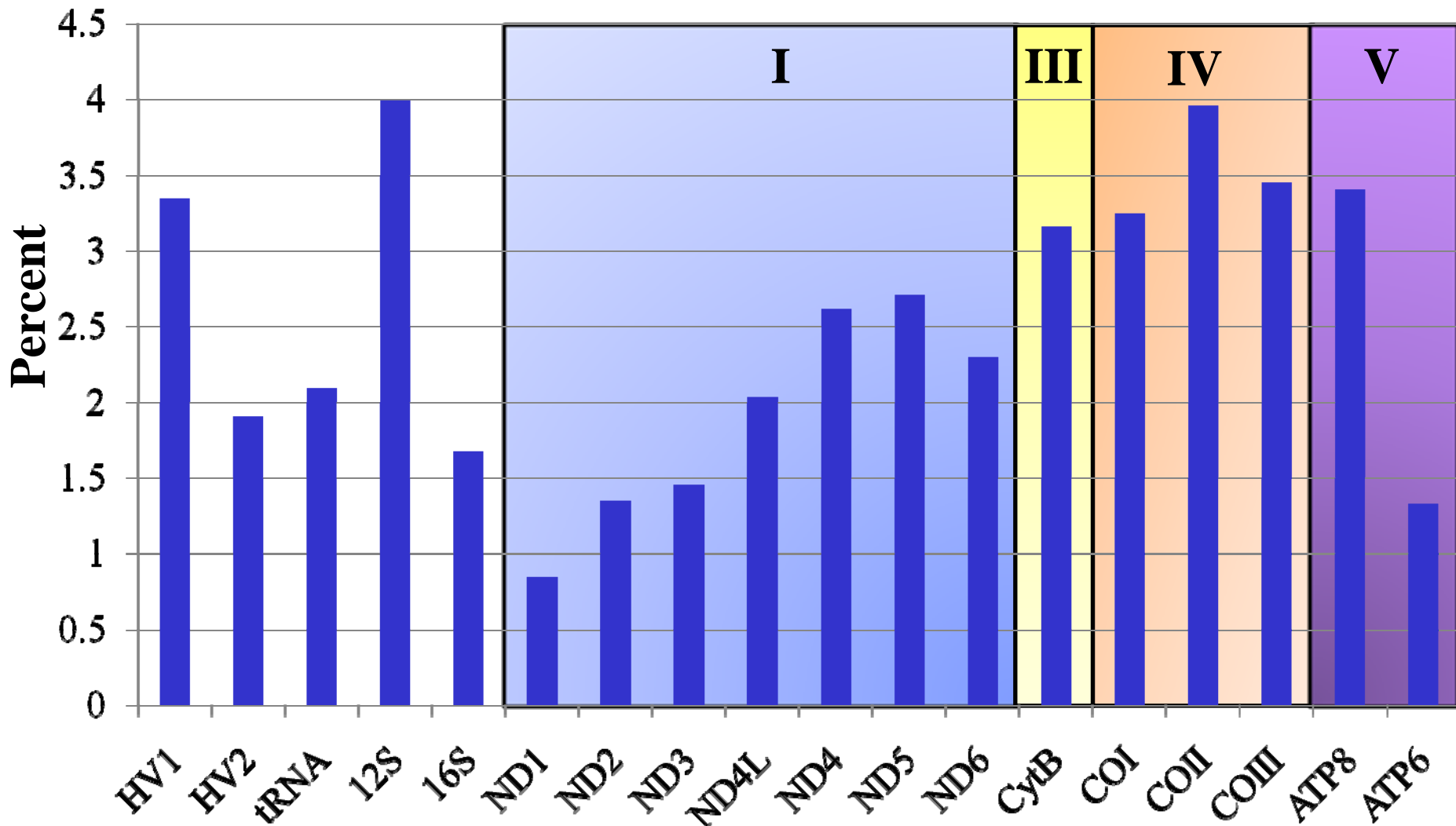
Percent of mtDNA heteroplasmic sites associated with RMR (p<0.05)

# Total Energy Expenditure (n=138)



Number of mtDNA heteroplasmic sites associated with TEE (p<0.05)

# Total Energy Expenditure (n=138)



Percent of mtDNA heteroplasmic sites associated with TEE (p<0.05)

## Summary

- I – Examining mtDNA variation for morbid conditions or traits is a neglected endeavor.**
- II – Requires knowledge of mtDNA evolutionary legacy.**
- III – Analysis has largely focused on haplogroups but the role of common variants, rare variants and heteroplasmy is mostly unexplored.**
- IV – Future studies will require large genetics consortia to comprehensively examine mtDNA associations with diseases and phenotypic traits.**
- V – Modeling mito-nuclear interactions is likely to yield new insights into the role of mitochondria in aging, disease, etc.**

