New genetic approaches in understanding susceptibility for metabolic syndrome in Mediterranean populations

(FP7-279171-1)  
2012 - 2015
MEDIGENE Objectives

Insulin resistance syndrome - metabolic syndrome (MetS) in immigrant populations in Europe (host and home countries)

Unravel new susceptibility genes for MetS considering the genetic variability (stratification) in case-control Genome Wide Association Studies (GWAS) and gene environment interaction

Finality: improve genetic markers (clinical scale); better explain heritability; offer a new basis for personalized medicine

Consortium of 13 countries in the Mediterranean area: clinical endocrinologists, geneticists, anthropologists and archeologists
Specificity of MEDIGENE

*Visceral obesity, hyperlipidemia, hypertension and diabetes*

*International Diabetes Federation (IDF)*

Questionable candidate for GWAS (*heterogeneous*)

Insulin resistance - unique feature (fundamental biological process)

MetS correlated with health indices in population (CV mortality)

<table>
<thead>
<tr>
<th>Host</th>
<th>Total</th>
<th>%</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>6,471,000</td>
<td>10.18</td>
<td>Algeria, Morocco, China</td>
</tr>
<tr>
<td>Spain</td>
<td>4,790,000</td>
<td>10.79</td>
<td>Romania, Morocco, Bolivia</td>
</tr>
<tr>
<td>Italy</td>
<td>2,519,000</td>
<td>4.28</td>
<td>Romania, Albania, Ukraine</td>
</tr>
<tr>
<td>Greece</td>
<td>974,000</td>
<td>8.66</td>
<td>Albania, Bulgaria, Romania</td>
</tr>
</tbody>
</table>

Modern migrations (immigration)

9% of world population, 8% of European community
Vulnerable, health status (assistance), low income
Relationship between migration and Health

Genetic background?

Modern, historical and ancestral migration
Modern migrations (Immigrants)

MEDIGENE populations

Albanese (Illyrians), Turkish (Altaic populations with Central Asians components), Romanian (Geto-Thracic populations from the Carpato-Danubian basin), North African immigrants (Berbers admixed with Bedouin tribes or Canaanite-Phoenicians in historical times) - Algerians, Tunisians and Moroccans.
Historical migrations in Mediterranean

Antiques Romans
(IV-I Century AD)
(n = 3800)
Archeo-genetics of Europe (Paleolithic)

Atlantic Ocean

Europe

Franco-Cantabrian Refugia

Azilian culture

Carpato-Danubian basin

Iberian-Maurusian culture

Capsian culture

Aterian culture

North Africa

Indo-Europeans

40 kya

20 kya

40 kya

40 kya
Haplotyping approach in MEDIGENE

Ancestral haplotype

Unphased DNA

Phased DNA

Haplotype 1

Haplotype 2

Haplotype 3

Haplotype 4

Haplotype 5

Recombination

Evolution

Natural selection

Genetic drift

Admixture

Rare SNP

Phylogeny

Classical GWAS (“frequentist”)
Working packages

140 genes

mtDNA
Y Chr

WP1 1st STAGE GWAS
600,000 SNPs

WP2 Ancient DNA study
In historical Romans

WP3 Locus refining

WP4 1st STAGE analysis
CC association in host countries

WP5 Epidemiology in host and home countries & novel recruitment for G x E interaction

WP6 2nd STAGE - Replication
Genotyping with filtered SNPs

WP7 2nd stage analysis and meta-analysis

WP8 Replication in Home countries

Filtered SNPs
Rare SNPs [mutation]
Methods of MEDIGENE

Next Generation Sequencing

Discovery

GS Junior (Montpellier) ➔ FLX 454

Genome Wide Association studies

Design of 600 000 SNP + 13 000 customized SNP

AXIOM Chip ➔ GeneTitan (Barcelona) ➔ Primary analysis

Bioinformatics & statistics

Mirrored ➔ Secondary analysis

Barcelona ➔ BC-platforms ➔ Montpellier

Data integration

Replication
Expected results

**New genes** or allelic variants specific to populations - may help diagnosis, treatment and predictive actions

Alternative for classical GWAS - considering *rare variants* (SNP) - ethnic specific and explaining better association (OR) and heritability in population

Explain a series of *epidemiological paradoxes* - e.g. lower mortality in immigrants from Maghreb in France (men but not women) - differences in MetS between North and South in France - low CV mortality in Greeks at the first generation - role of the Mediterranean diet

Alternative explanation of *insulin resistance* - energy allocation mechanism versus adaptation of humans in relation with fertility, population density, social competitiveness, rural to urban transition
Consortium

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Perspectives and ethical considerations

Understanding the way of life of different people in native countries, consideration of their way of life, natural (ancestral) ecological niche, consequences of migration in a broader perspective as a potential factor of global increase in prevalence of diabetes/obesity, impact of deregulation of food supplies in modern times.

Human genetic diversity is a source of persistence and increase in the differences in health seen in various EU citizens disadvantaged by inequalities and low-income. Understanding and accepting human genetic diversity, in opposition to biological egalitarianism represents a major advance in current thinking and a positive attitude. Group differences will help to understand how genetic and environmental factors produce biological outcomes. We should bear in mind that genetic diversity is a virtue of mankind not a defect, and a source of evolutionary resilience and adaptation assuring survival and health with potential positive economic consequences on agriculture and environment.