The GEHA (Genetics of Healthy Ageing) contribution to the Italian Hub of Population Biobanks (HIBP)

Elisa Cevenini
Federica Sevini - Claudio Franceschi
GEHA - Genetics of Healthy Aging
Integrated Project of EU 6thFP

25 Partners
Recruitment and Genome Scanning
(nuclear and mitochondrial genomes)
of 2650 90+ sibpairs and 2650 young controls
collected in 11 countries
May 1st 2004 - April 30th 2010
(www.geha.unibo.it)

Coordinator: Prof. Claudio Franceschi

(Franceschi et al., Ann. NY Acad. Sci., 2007)
GEHA major objectives (1):

to identify genes that influence healthy aging and longevity in humans, and that protect individuals from major age-related diseases and disabilities, thus allowing them to survive to advanced old age in good cognitive and physical condition.
GEHA major objectives (2):

• To perform a genome-wide scan on the DNA of all recruited sibpairs (ASP analysis);

• To fine-map the chromosomal regions identified by ASP analysis and the three candidate regions (D4S1564 in chromosome 4, 11p15.5 in chromosome 11 and around the ApoE gene in chromosome 19) by means of large scale association studies;

• To verify the role of mitochondrial DNA (mtDNA) germline variants (haplogroups, subhaplogroups), and mutations (C150T) in human longevity, and to study their interaction with the newly emerging longevity nuclear genes;

• To stratify the samples according to ApoE genotype, i.e. the only genetic marker found to be associated with longevity;

• To develop innovative analytical strategies (based on statistical method and mathematical models) capable of combining all the data collected (demographic, clinical, socio-economical, genetic and related to lifestyle), to highly increase the power of genetic analysis;

• To perform a longitudinal study to evaluate the importance of genetic factors on mortality of the recruited 90+ sibpairs.
The area of the circles indicates the amount of recruitment burden within GEHA. The same color identifies units which will recruit sibpairs in the same countries.
GEHA Study Design

(Skytthe et al., Exp Gerontol., 2011)
GEHA Population (Biobank)

Europe:
11 countries, 15 recruitment centres

Population size:
- 5381 90+ subjects belonging to 2537 families
- 2537 younger controls

GEHA contribution to HIBP:
3 recruitment centres: Bologna, Rome and Calabria

Population size:
- 1170 90+ subjects (age range: 90-106 years; 5% > 100 years of age) belonging to 541 Italian Nonagenarian families recruited in Northern, Central and Southern Italy:
  - 31.9% males and 68.1% females (mean age: 93.4 and 93.8 years)
- 541 younger controls

Recruitment period: November 2004 – July 2008
GEHA Biological material

- Whole Blood
- Plasma
- Serum
- Granulocytes
- PBMCs

Cryopreservation: LN$_2$ system

Automated platforms for liquid handling of biological samples:

- Tecan Freedom Evo
- Hamilton MicroLabStar
1. To compare the phenotypic characteristics of the Italian 90+ siblings recruited in Bologna, Rome and Calabria.

2. To assess the Italian 90+ siblings as far as their health/functional status is concerned in order to define the healthy aging phenotype and to identify the parameters characterizing their health status.

3. To perform a survival analysis by using mortality data at January 1st, 2010 to identify the predictors of survival.

4. To investigate the concordance of health and functional status among 90+ siblings to discover which variables are influenced by familiarity/genetics.

(Paper in preparation)
GEHA Genotypic data

- **Genome wide scan** using 6000 SNPs on an Illumina high throughput platform (Centre National de Genotipage, Paris) on all 90+ sib pairs
- **Genotyping** of 400 tagSNPs on 11p15.5 chromosomal region (2.4Mb) using 600 90+ unrelated sibs and 600 controls (samples from Bologna, Ancona, Kiel, Cosenza)
- Analysis of **ApoE polymorphisms** on all 90+ sib pairs and controls

1. **Linkage Analysis** on 2118 nonagenarian Caucasian siblings: 4 regions show linkage with longevity (1 region includes APOE locus)

2. **Association analysis** using GWAS data in a subgroup of 1,228 90+ unrelated sibs and 1,907 geographically matched controls: confirmation that **APOE locus is a longevity gene** and that in the other 3 regions there are additional longevity loci

*(Paper in preparation)*
GEHA mtDNA data

- mtDNA haplogroups and subhaplogroups from 2650 sibpairs probands and 2650 younger controls (in all sibpairs the entire D-loop region, 1121 bp, will be sequenced)
- The entire mtDNA sequence (16569 bp) of ~1300 sibpairs probands and younger controls

(Paper in preparation)

- Evaluation of percentage of heteroplasmy of C150T mutation/polimorphism in 96 sibpairs and 96 younger controls

Somatic Point Mutations in mtDNA Control Region Are Influenced by Genetic Background and Associated with Healthy Aging: A GEHA Study

Giuseppina Rose¹, Giuseppe Romeo¹, Serena Dato¹, Paolina Crocco¹, Amalia C. Bruni², Antti Hervonen³, Kari Majamaa⁴, Federica Sevini⁵, Claudio Franceschi⁵, Giuseppe Passarino¹*, the GEHA Project Consortium¹
**GEHA Databases**

- **Phenotypic Database** (location: Odense, Denmark)
- **Genetic database** (location: Kiel, Germany)
- **mtDNA Database** (location: Bologna, Italy)

Physisically separated, but interconnected in order to:
- allow all types of analysis (cross-analysis)
- protect privacy

Access to whole data is restricted to GEHA partners until the end of the project, after authorization of the Steering Committee.
GEHA is one of the Population Biobank founders of the HIBP

- **GEHA younger controls (50-75 yrs):**
  possibility to enlarge Italian population of middle aged and elderly subjects, to be included in new studies

- **GEHA 90+ siblings:**
  possibility to enlarge a peculiar Italian population of long-lived subjects, rare and difficult to recruit
La giovinezza è felice perché ha la capacità di vedere la bellezza. Chiunque sia in grado di mantenere la capacità di vedere la bellezza non diventerà mai vecchio

-Franz Kafka-