Proceedings of the Joint Meeting AGI-SIBV-SIGA
Assisi, Italy – 19/22 September, 2011
ISBN **978-88-904570-2-9**

Poster Communication Abstract – 9.49

A MULTILOCUS ANALYSIS SHOWS THE ROLE OF GENETIC VARIABILITY OF GENES INVOLVED IN METABOLIC PATHWAYS IN HUMAN LONGEVITY

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Longevity, metabolic pathways, multilocus longevity

Many studies on both animal models and humans have shown that metabolic pathways (INS/IGF-1; GH; cell cycle; metabolism of xenobiotics etc.), conserved along evolution, play a crucial role in lifespan extension. In order to highlight if, and to what extent, the variability of the genes involved in metabolic pathways affects human longevity we examined the variability of numerous genes involved in these pathways in a population from Calabria.

The study was a two step multilocus association analysis to detect genetic variants that affect human longevity. The sample analyzed was composed of 991 (514 female and 476 males; age: 50-104), unrelated subjects from Calabria. About 15% of the samples (149 subjects: 69 cases and 64 controls) were analyzed in Stage 1 for 305 SNPs (Single Nucleotide Polymorphisms) belonging to 105 genes selected from different metabolic pathways (INS/IGF-1; GH; cell cycle; metabolisms of xenobiotics; stress response and Neuro active ligand-receptor interaction). In Stage 2 we have genotyped the remaining samples (240 cases and 529 controls) for 27 [0]SNPs selected from those belonging to Stage 1. Both dataset were analyzed for association with longevity by using MAX3 test.

We found that two polymorphisms were associated with longevity. One is located in a gene that codifies for a protein member of the serine/threonine protein kinase family. This kinase mediates the signaling transduction and controls a variety of cell functions including transcription and apoptosis. A second polymorphism associated [0]with longevity falls in a gene that is a member of the glutathione S-transferase (GSTs) super-family. These proteins have a crucial role in metabolisms of xenobiotic and in particular in the detoxification of carcinogens, mutagens. Moreover, it is also involved in the response to oxidative stress. This polymorphism is located in the intronic region (introne 1), very close to the 5'UTR region. So it is possible that this polymorphism falls in a regulatory region (for example a transcription factor binding region) or that is in LD with another functional SNP. HapMap data shows that this SNP is in a strong linkage with other polymorphisms located in intronic region or in 5'UTR region.

Future studies are needed to better explain the role of this polymorphism in longevity.