

LECTURE PRESENTATION

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Genetics of longevity

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Epidemiological and family-based studies in different populations underlined the existence of a genetic component in human longevity.

Studies on families of centenarians demonstrated that parents, siblings and offspring of long-lived subjects have a significant survival advantage. In particular, the survival curve of siblings of centenarians is significantly higher than that people belonging to the same birth cohort. Moreover, siblings of centenarians have a lower risk of suffering from major age-related diseases, such as cardiovascular diseases, diabetes and cancer, when compared to appropriate selected controls from the same population. Indeed, studies on the concordance of the age of death in twins demonstrated a higher correlation in monozygotic than dizygotic twins and suggested that approximately 25% of the variation in adult lifespan is caused by genetic differences between individuals. It was also demonstrated that the genetic component affecting longevity increases at advanced ages and it is generally stronger in males than in females. Furthermore, a positive correlation between population homozygosity and longevity was suggested, confirming the relevance of genetic differences between individuals for the susceptibility to a long lifespan.

Identifying genes that affect human longevity can provide information about the molecular mechanisms involved in the aging process and shed light on the heterogeneity of the aging phenotype. Studies on experimental models suggest that caloric restriction improves age-related health and slow the aging process by limiting energy intake. Furthermore, in animal models specific alterations in single genes (*age-1*, *daf2*, *sir2*, *methusela*, *p66*) can dramatically extend or decrease lifespan. In humans, evidence is accumulating for an additive multi-locus model, i.e. multiple genes with modest effect, working independently and as a network [1]. Because of the suggested additive effects of different genetic

variants predisposing to longevity, the combined approach of linkage analysis in affected sib pairs (ASP) in candidate regions for high frequent variants and Genome Wide Association for less frequent polymorphisms [1] is considered promising for the identification of the genetic component of human longevity. Among the genes for which association has been demonstrated with human longevity, there are Apolipoprotein genes (APOE, APOB, ACE, APOC3), sirtuin genes (SIRT1 and SIRT3), genes belonging to the anti-oxidant (SOD1, SOD2, PON1, FOXO3A) and inflammatory pathways (Klotho, CETP, IL6). A relevant role seems to be represented also by the inherited and somatic variability of the mitochondrial genome.

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