

The centenarian Epigenome: DNA methylation and chromatin Formation of the Oldest Old

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Extended Abstract

Statement of the Problem: The aging process is generally associated with multi system deterioration that leads to the development of various chronic diseases which greatly affect the lifespan as well as quality of life of the aging individual. Advances in medical care have promoted lifespan beyond twice as much as reproductive age, yet a genomic explanation to the survival of centenarians is not yet available, despite extensive genomic research performed. We hypothesize that the centenarian epigenome might offer an explanation through epigenetic flexibility of methylation and chromatin structure. Such an approach is novel and has not yet been implemented on human populations. Aim: The aim of our study is to characterize the aging epigenome and chromatin configuration in order to demonstrate this epigenetic flexibility which possibly allows crafting an appropriate genomic response, best fit to the environment. Methodology & Theoretical Orientation: Three groups of participants are currently being recruited (up to 100 participants each); centenarians (95+ yo), offspring of centenarians, controls (65-80 yo). Peripheral blood is drawn from all participants for epigenetic analyses. Illumina Infinium Methylation EPIC array is used on DNA from CD34+ cells of all participants and Hi-C analyses are performed on age and sex matched grouped white blood cell samples. Findings: Based on previous work led by Prof. Gil Atzmon we expect to find differential methylation patterns among the groups. Specifically, we observe ENCODE hot spots among centenarians and offspring, which are distinctly different in methylation status from controls. In addition, using unrelated samples we aim to highlight structural differences between the centenarian and non-centenarian related controls' chromatin. Our approach avoids small scale variance and emphasizes the bigger biological differences in chromatin formation associated with age.

Figure 1: Unsupervised clustering of methylation data (25,000 loci) from CD34+ cells shows differences in methylation between Centenarians and Controls. The heat map shows hypomethylated loci in red, hypermethylated in yellow. Distinct patterns are obvious between those over 100 and those who are 80 or 60 years old.

Recent Publications: 1. Ben-Avraham D, Govindaraju D R, Budagov T, Fradin D, Durda P, Liu B, Ott S, Gutman D, and Atzmon G (2017) The GH receptor axon 3 deletion is a marker of male-specific exceptional longevity associated with increased GH sensitivity and taller stature. *Science Advances* 3(6):e1602025. 2. Ben-Avraham D, Karasik D, Verghese J, Lunetta K L, Smith J A, Eicher J D, Vered R, Deelen J, Arnold A M, Buchman A S, Tanaka T, Faul J D, Nethander M, Fornage M, Adams H H, Matteini A M, Callisaya M L, Smith A V, Yu L, De Jager P L, Evans D A, Gudnason V, Hofman A, Pattie A, Corley J, Launer L J, Knopman D S, Parimi N, Turner S T, Bandinelli S, Beekman M, Gutman D and Atzmon G (2017) The complex genetics of gait speed: genome-wide metaanalysis approach. *Aging* 9(1):209-246.

3. Sharvit L, Gutman D, Adwan H, Vered R and Atzmon G (2016) Genetics of age-dependent human disease. *Hazzard's Geriatric Medicine and Gerontology*, 7e, chapter 2. 4. Gutman D, Sharvit L and Atzmon G (2014) Possible Mechanisms for Telomere Length Maintenance in Extremely Old People. *Hereditary Genet* 3:e111

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