

LUCIA SCISCIOLA

Invecchiamento e Gender: il ruolo dell'Epigenetica



Roma, 30 novembre - 3 dicembre 2022 UNIVERSITÀ CATTOLICA DEL SACRO CUORE



DICHIARO

CONGRESSO NAZIONALE SIGG

LA LONGEVITÀ DECLINATA AL FEMMINILE

di non aver avuto, negli ultimi due anni, alcun rapporto, anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario



AGING

MOLECULAR MECHANISMS OF CELLULAR AGING





J Invest Dermatol. 2021 Apr;141(4S):951-960. doi: 10.1016/j.jid.2020.11.018



AGING DISPLAYS SEXUAL DIMORPHISMS



MAN

FEMALE

WHO, https://www.who.int/data/gho/data/indicators/indicator-details/GHO/life-expectancy-at-birth-(years)



WOMEN LIVE LONGER THEN MEN







PARADOXICALLY THEY SUFFER GREATER MORBIDITY PARTICULARLY LATE IN LIFE



Gender differences in healthy life years within the EU: an exploration of the "health-survival" paradox

Herman Van Oyen · Wilma Nusselder · Carol Jagger · Petra Kolip · Emmanuelle Cambois · Jean-Marie Robine



*: m = males, w = women

le_m, le_w: life expectancy men, women hly_m, hly_w: healthy life years men, women uly_m, uly_w: unhealthy life years men, women *: dif_le: gender difference (women minus men) in LE dif_hly: gender difference in HLY mef_hly: mortality effect gender difference in HLY

def_hly: disability effect gender difference in HLY

dif_uly: gender difference in ULY

mef_uly: mortality effect gender difference in ULY

def_uly: disability effect gender difference in ULY



FRAMEWORK OF THE COMPLEX INTERACTIONS BETWEEN MOLECULAR, CELLULAR, FUNCTIONAL, ORGAN, AND WHOLE BODY AGING PROCESSES ACROSS THE LIFE COURSE IN MEN AND WOMEN



Elife. Volume 10, 13 May 2021. doi: 10.7554/eLife.63425.



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HUMAN BIOMARKER OF AGING	SEX-SPECIFIC EFFECTS	REFERENCES
Genetic Factors In Aging	sex chromosomes, X-chromosome inactivation in woman, Loss of Y in men, Transcription regulation	Bernabeu 2020; Forsberg, 2017.
Cellular senescence	More senescent cells in male mice compared to female	Yousefzadeh et al., 2020
Proteostasis and autophagy	Higher proteasomal activity in female mice	Jenkins et al., 2020
Telomeres	Longer telomeres in woman	Factor-Litvak et al., 2016
Mitochondrial linked mechanisms	Better respiratory function in woman; Mutation accumulation; higher mtDNA abundance in woman	Hagg et al., 20202; Demarest and McCarthy et al., 2015
Epigenetics	Higher epigenetic age in men; Genome-wide DNA methylation	Horvath et al., 2016; Klein et al., 2019

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MECHANISMS OF EPIGENETIC REGULATION



- Histone modifications (acetylation, methylation)
- **DNA** methylation

Mol Psychiatry. 2020 Aug;25(8):1718-1748. doi: 10.1038/s41380-019-0601-3.

Cell Res 28, 507-517 (2018). https://doi.org/10.1038/s41422-018-0034-6v

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GENOME-WIDE METHYLATION PROFILES REVEAL QUANTITATIVE VIEWS OF HUMAN AGING RATES



Molecular Cell

QUANTITATIVE MODEL OF AGING

using measurements at more than 450,000 CpG markers from the whole blood of 656 human individuals, aged 19 to 101.

methylation markers that increased with age methylation markers that decreased with age

Mol Cell. 2013 Jan 24;49(2):359-367. doi: 10.1016/j.molcel.2012.10.016.

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Genome Biol. 2013;14(10):R115. doi: 10.1186/gb-2013-14-10-r115.

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THE PRINCIPAL GENES AFFECTED BY DNA METHYLATION CHANGES DURING AGING

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Gene	Methylation pattern	Functional association	Species	Author
LINE-1	↑ in loci	Stem cell exhaustion	M. musculus	Hernando-Herraez et al. (2019)
<i>C1Q13</i>	↑ in CpG island	Ageing and cancer	M. musculus	Mozhui and Pandey (2017)
			H. sapiens	
SRD5a2	↑ in CpG island	Ageing and cancer	M. musculus	
			H. sapiens	
PTK7	↑ in CpG island	Ageing and cancer	M. musculus	
			H. sapiens	
MGMT	↑ in promoter region	Age-related cataract	H. sapiens	Li et al. (2014)
ERCC6	↑ in promoter region	DNA repair	H. sapiens	Wang et al. (2016)
PRC2	↑ in locus	Age-related regulation of the methylome	M. musculus	Beerman et al. (2013), Sun et al. (2014), Benayoun et al. 2015), Dozmorov (2015) and Mozhui and Pandey (2017)
EIF5, KLF3 PTPRA	↑ in CpG island ↓ in CpG island	Overexpression of <i>SIRT1</i> mimicking the effects of caloric restriction	In silico and human intestinal Caco-2 cell line	Ions et al. (2013), Buler et al. 2016) and Watroba et al. (2017)
EIF5, STK10	↑ in CpG island	Reduced SIRT1		
IRX3, PTPRG, TBX3	↓ in CpG island	expression mimicking the effects of ageing		
Lipid metabolism genes	Delays age-related pattern	Caloric restriction	M. musculus	Hahn et al. (2017)
Imprinted genes	↑ in locus	Loss of insulin/IGF-1 signaling	M. musculus	Boucher et al. (2014)
Global DNA	↑ MTHFR 677CC genotype	Supplementation with folic acid + vitamin B_{12}	H. sapiens	Sae-Lee et al. (2018)

Biogerontology. 2020 Aug;21(4):423-443. doi: 10.1007/s10522-020-09874-y.



EPIGENETIC CLOCK: A MEASURE OF AGING SPEED



DNA methylation changes that occur with aging are not purely stochastic, but rather follow a predefined pattern that is constant across individuals and populations

Genome Biol. VOLUME 14, 2013 doi: 10.1186/gb-2013-14-10-r115

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THE EPIGENETIC ROLE?



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SEX-RELATED DIFFERENCES IN EPIGENETIC AGING RATES

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> 77 Male

Female

"Faster ticking" epigenetic clock in men

EXPLORATORY ANALYSIS OF AGE AND SEX DEPENDENT DNA METHYLATION PATTERNS ON THE X-CHROMOSOME IN WHOLE BLOOD SAMPLES

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1.00 0.75 <u>0</u> 0.50 -0.25 0.25 0.75 0.50 1.00 Male mear

A: CpGs more methylated in females

B: very low methylation levels and not significant in both sexes.

C: very high methylation and similar in both sexes

D: more methylated in males

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DT			
ed	55	123	293
T	34.59	22.91	21.56
T	13.25	9.10	26.02
eometric test p	7.89e-46	3.30e-67	3.22e-105
tion			
validated (FDR < 0.05)*	3	16	24
ated	5.45	13.01	8.19
R < 0.05	314	591	2781
testing all CpGs on chromosomes	X or 20 in LBC1921 I	birth cohort	

Genome Med, Volume 12, 2020, https://doi.org/10.1186/s13073-020-00736-3



*FDR from

Genome Medicine



AGE-DEPENDENT DNA METHYLATION PATTERNS ON THE Y CHROMOSOME IN ELDERLY MALES



219 significant CpG sites with >82% of them hypermethylated with increasing age

Aging Cell

Open Acce

Aging Cell, Volume: 19, Issue: 2, First published: 21 February 2019, DOI: (10.1111/acel.12907)

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THE PRINCIPAL GENES ON SEXUAL CHROMOSOME AFFECTED BY DNA METHYLATION CHANGES DURING AGEING

Gene	Chromosome	Function
KIAA1210	X (both female and male)	Spermatogenesis
TAF7L	X (both female and male)	Spermatogenesis
PLXNB3	X (both female and male)	Axon guidance
TSC22D3	X (both female and male)	T-cell regulation
PRKY	Y	Kinase pseudogene
NLGN4Y	Y	Neuronal development and synaptic transmission
		Epigenetics Chromatin. 2021 Jul 2;14(1):33. doi: 10.1186/s13072-021-00407-6

Genome Med 12, 1 (2020). https://doi.org/10.1186/s13073-019-0693-z



AGE-RELATED DNA METHYLATION CHANGES ARE SEX-SPECIFIC: A COMPREHENSIVE ASSESSMENT





sDMPs: Sex- associated differentially methylated positions aDMPs: Age-associated differentially methylated positions saDMPs: Sex- and age- associated differentially methylated positions

Continued

Aging (Albany NY). 2020 Dec 3;12(23):24057-24080. doi: 10.18632/aging.202251.



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Continued



FIGN: ATP-dependent microtubule

PRR4: Proline-rich protein 4

Aging (Albany NY). 2020 Dec 3;12(23):24057-24080. doi: 10.18632/aging.202251.



CONCLUSIONS

- CpG sites display differences in age-associated DNA methylation patterns between males and females
- The majority of differences in age-associated methylation trajectories between sexes are present not only in sexual chromosomes but also in autosomal one





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THANK YOU