Human Longevity

(Has genetic research provided any advances to increase human longevity?)

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SUMMARY:

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Abstract

Over the years longevity has increased drastically from a 50yr life span to 75 yrs as an average globally. This clearly highlights the effect of extrinsic factors such as nutrition , physical activity and medical advances (antibiotics, therapeutic care, etc) on longevity in humans.However ,
There are important intrinsic factors that contribute to long life as well, therefore this paper seeks to answer : Has genetic research provided any advances to increase human longevity?

In this paper I have summarized the internal and external causes of longevity, laying emphasis on gene impact, meta-analyses of centenarian phenotype, clinical trials, and animal models tests to the development of longevity drugs for healthy aging in humans. I also briefly talk about the current advancements that may help scientists succeed in this field in the near future.

The Key areas of focus in this paper are the role of telomeres, DNA Methylation, Mutations (suppression or prominence of genes or alleles),aging diseases and also the demography and heredity from centenarians.I have also talked about the advances in longevity pharmacology .

Keywords

Telomere length,longevity,centenarians,DNA Methylation,Gene modification,IGF,longevity drugs
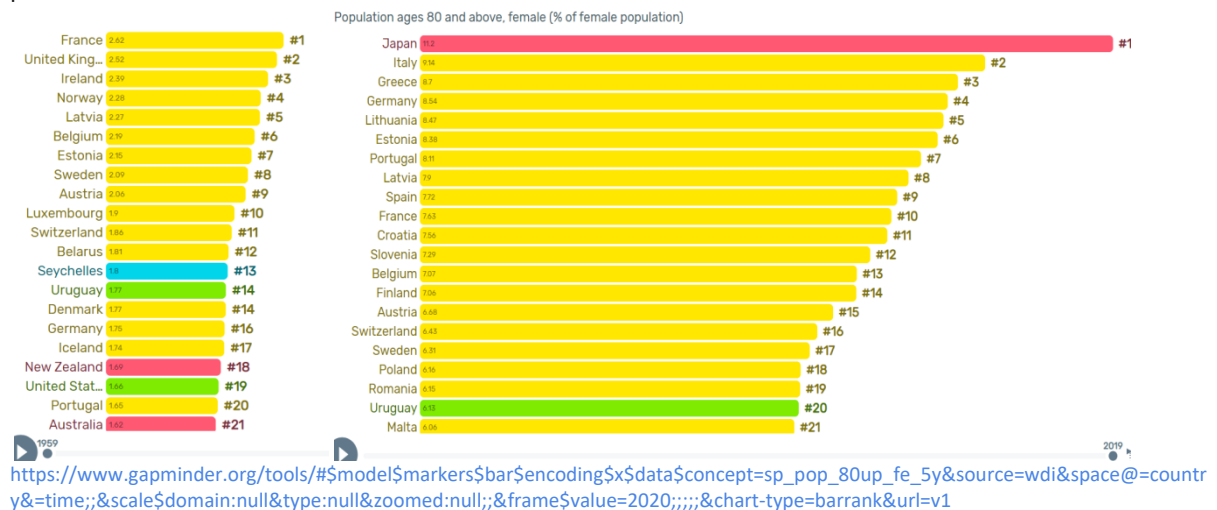
Introduction

Long life is fascinating.As people reach their 60s they begin to think they are reaching the end of life but is this true? Well, maybe before but not anymore "Life expectancies in developed and developing countries alike have been rising continuously, causing the number of people who live to 100 years to rise also" (Buchholz, 2021).

There is a lot of science behind the process of healthy aging and longevity, as people are ambitious to become the next "Jeanne Calment." Jeanne Calment's still-unmatched, validated human life span of 122 years and 164 days, over 3 years longer than any other, surprises many While her case is broadly accepted as a golden standard of validation, her record age still raises skepticism among some (Champigneul, 2020). People tend to follow what they see in the media - like news articles titled "this is what the longest aged people eat, (OR) follow this diet to live longer…." while food, exercise, behavior do have a significant impact on life of centenarians " Gerontologists have identified a variety of positive attributes, such as not smoking, small body size, diet, regular exercise, avoidance of stress, lifestyle, family connectedness, avoidance of worry, and a positive attitude toward life" (Thomas, 2017). "People with a low-risk behavioral profile had a 65% lower mortality rate than those with a high-risk behavioral profile" (Brian et al, 2018). The media cannot always be trusted.

Recently, the term "Blue Zone" has been trending but what actually is it? Dan Buettner, Blue Zones founder, is a National Geographic Fellow and multiple New York Times bestselling author. He has discovered five places in the world – dubbed Blue Zones – where people live the longest, and are healthiest: Okinawa, Japan; Sardinia, Italy; Nicoya, Costa Rica; Ikaria, Greece, and Loma Linda, California" (Blue Zones, 2022).Thus studying the genetic composition and phenotype of people in this area would help understand longevity better.

To understand this better I observed the rise in female centenarians (See Fig 1) and male centenarians (See Fig 2) through graphs over the past 60 years using GapMinder. In 1959, the global average lifespan of women was 55yrs and men was 51yrs however, by 2019, the average lifespan had increased dramatically to a 75 yrs life span in women and 71 yrs in men , these changes were even more pronounced by country (World bank,2022).

Fig 1: Change in Longevity by Country for Females, 1959-2019 (GapMinder, 2022). Shown here are longevity rankings by country for women in 1959 and 2019; for the full video of rankings by year during this time period, please click on the link below.

https://www.gapminder.org/tools/#$model$markersbarencoding$x$data$concept=sp_pop_80up_fe_5y&source=wdi&space@=country&=time;;&scale$domain:null&type:null&zoomed:null;;&frame$value=2020;;;;;&chart-type=barrank&url=v1

Having observed that centenarians are most common in countries with mediterranean diets and japan ofcourse with a japanese diet , it is hypothesized that they contribute to longevity
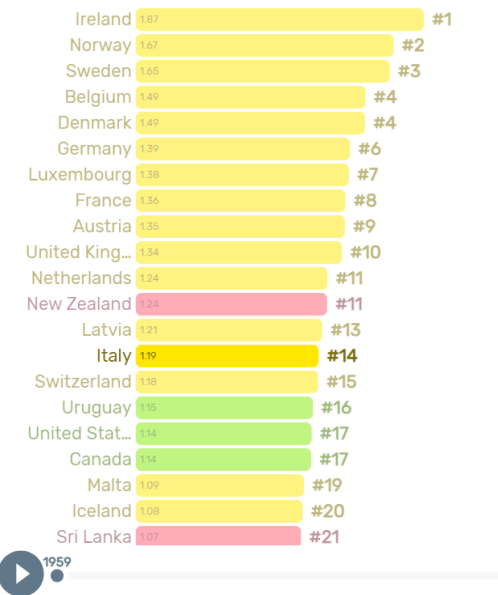
We find that a Mediterranean diet can reduce risk of death by 8%. The EPIC Elderly Study which included information of over 74,000 Europeans showed that adherence to a Mediterranean diet was associated with lower all cause mortality (MDR,2022).

The diet includes certain ingredients that have been associated consistently with longevity, better heart and cognitive health. The "longevity ingredients" in this eating pattern are vegetables, plants in the form of greens and herbs, legumes, fish, dairy from free-range animals, olive oil as the main source of fat, very little meat and a bit of alcohol. There are several studies that have associated the Mediterranean diet with a longer life (MDR,2022).
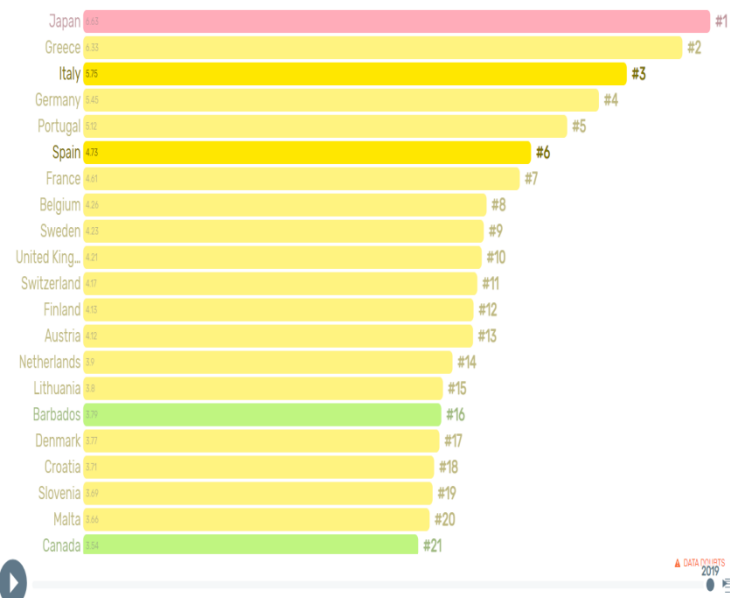
The rise of the Japanese centenarian is also for the mainly for same reason-DIET .- "Among the G7 countries, Japan has the highest life expectancy at birth according to 2016 OECD data, particularly for women" "The higher life expectancy of Japanese people is mainly due to fewer deaths from ischemic heart disease and cancers, particularly breast and prostate cancer. This low mortality is mainly attributable to a low rate of obesity, low consumption of red meat, and high consumption of fish and plant foods such as soybeans and tea "(Juneau,2021).

Fig 2: Change in Longevity by Country for Males, 1959-2019 (GapMinder, 2022). Shown here are longevity rankings by country for men in 1959 and 2019; for the full video of rankings by year during this time period, please click on the link below.

Population ages 80 and above, male (% of male population)

Country	Value	Rank
Ireland	1.87	#1
Norway	1.67	#2
Sweden	1.65	#3
Belgium	1.49	#4
Denmark	1.49	#4
Germany	1.39	#6
Luxembourg	1.38	#7
France	1.36	#8
Austria	1.35	#9
United King…	1.34	#10
Netherlands	1.24	#11
New Zealand	1.24	#11
Latvia	1.21	#13
Italy	1.19	#14
Switzerland	1.18	#15
Uruguay	1.15	#16
United Stat…	1.14	#17
Canada	1.14	#17
Malta	1.09	#19
Iceland	1.08	#20
Sri Lanka	1.07	#21

▶ 1959

Population ages 80 and above, male (% of male population)

Country	Value	Rank
Japan	6.63	#1
Greece	6.33	#2
Italy	5.75	#3
Germany	5.45	#4
Portugal	5.12	#5
Spain	4.73	#6
France	4.61	#7
Belgium	4.26	#8
Sweden	4.23	#9
United King…	4.21	#10
Switzerland	4.17	#11
Finland	4.13	#12
Austria	4.12	#13
Netherlands	3.9	#14
Lithuania	3.8	#15
Barbados	3.78	#16
Denmark	3.77	#17
Croatia	3.71	#18
Slovenia	3.69	#19
Malta	3.66	#20
Canada	3.54	#21

⚠ DATA DOUBTS 2019

▶

https://www.gapminder.org/tools/#$model$markersbarencoding$selected$data$filter$markers@=ita&=est&=esp;;;;&x$data$concept
=sp_pop_80up_ma_5y&source=wdi&space@=country&=time;;&scale$domain:null&type:null&zoomed:null;;&frame$value=2020;;;;;&cha
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Another notable observation is that women centenarians are significantly higher - "Women do not live longer than men because they age more slowly, but because they are more robust at every age.People who have lived to be >110 years old are called supercentenarians. Of the ~560 supercentenarians we know of worldwide, almost 90% are women".This is not surprising simply because of the many present in the female bodies - ''female hormones and the role of women in reproduction have been linked to greater longevity. Estrogen, for example"(Austad,2006).

Apart from all this there are so many internal factors that contribute to longevity.In this article the genetic and epigenetic factors have been summarized in detail to give us an idea how scientists are developing in the field of longevity and "longevity pharmacology." So this research seeks to answer whether genetic research has provided any advances to increase human longevity?

Methods

I conducted archival research on genetic applications to extend human longevity in the following databases (Google Scholar, PubMed), using the following search terms (list them here), as well as general searches on longevity in the public venue using broad internet searches and publicly available data using visualization tools (Google, GapMinder).

Analysis of the role of genetics in longevity

Several intrinsic factors have been explored that may contribute to the development of drugs/mechanisms in extending longevity in humans, including: telomere length, DNA methylation, genetic polymorphisms, insulin growth factors, and the role of genes in diseases.

Some studies are conducted on human populations or use human tissues, such as those using centenarians from different geographic locations and comparing their phenotype to younger population and/or the next generation of the same family, or studies using genome-wide association studies (GWAS) to help scientists identify genes associated with a particular disease (or another trait). Many studies reviewed use animal models, like fright flies, worms (*C.elegans*), and rats (such as spalax and Naked Mole Rat).

1.Role of telomere

Telomere length is heritable, and genetic variations that affect telomeres may affect lifespan. Telomeres, the caps that protect the end of linear chromosomes, are known to shorten with age, inducing cell senescence and aging, while many studies have proved that the shortening of telomeres can serve as an important biomarker (biological thermometer) for life history, better than chronological age, its status as a biomarker of human aging is not settled (Shawi and Autexier 2008; Mather et al, 2011). Recent studies have suggested that telomere-induced senescence may occur irrespective of the length of telomeres and that the rate of increase in the percentage of short telomeres rather than the overall telomere length can predict lifespan .
Studying telomere dynamics in long-lived in particular would help understand the mechanisms they developed that help actively postpone senescence and encourage defense against the deteriorating effects of aging processes.

In humans, telomere length is of the order of 0.5–15 kilobase pairs.As the length of telomere declines the cells lose several important genes that cause them to enter a phase known as "Replicative phase " ,this shortening in the somatic cells is due to the "end-replication problem" (Harley,1991)."The telomeres can also be corrupted by various DNA damages and oxidative stress. caloric restriction may cause oxidative damage that leads to telomere shortening.Autosomal dominant dyskeratosis congenita, is caused by mutations in the gene (hTR) for the RNA component of telomerase that result in shortened telomeres

Telomere length is also heritable, with heritability estimates ranging from 44 to 80% (Slagboom et al. 1994; Andrew et al. 2006). Long-lived individuals and their offspring maintain longer telomeres compared with controls (Atzmon et al, 2010).

Telomeres have been studied in animals like the Naked mole rat (Heterocephalus glaber/NMR) and Blind mole rat (spalax). These are long lived organisms unlike mice and exhibit extreme longevity of up to 30 years and 20 years respectively.In these organisms telomeres don't shorten in dying

cultured cells, when compared to humans hence we can conclude that what affects longevity is the length and not number of telomeres(Adwanet al,2019).

When studying these organisms, the relative telomere length was measured in blood cells (peripheral blood leukocytes) cells, this is the same method used in human tests as well as it is not only the most convenient method but also due to the ability to obtain multiple repeated samples using minimally-invasive sampling techniques(Kim et al,2012).

1.1 Telomere with respect to age and gender

(Adwanet al,2019).It's evident that the telomere length would vary with age , one of the most common explanations to this is the rise in loss of telomeres by stressors like oxidative stress.In Spite of being subjected to extremely stressful environments with low oxygen ,high carbon dioxide ,the NMR have high tolerance to hypoxia and hypercapnia therefore become resistant to damage by reactive oxygen species(ROS)which explains why their telomeres do not shorten with age however when spalax was subjected to the same living conditions, rTL decreased with age in kidney, muscle and lung of Spalax with a higher rate in muscle,unlike in NMR where somatic tissues express telomerase activity and established that highly proliferative tissues(lung and kidney) have faster decline in telomere length with age than in minimally proliferative tissues such as muscle .Various studies in humans have also remarked that rtls of females are more than males.which is consistent with their increased longevity compared to males moreover our results showed a positive correlation between telomere length and age only in males but not in females. One possible cause is that female NMRs might rely on other mechanisms than telomerase for maintaining telomere length like recombination that occurs in long telomeres; however this result may also be due to bias in the study(Adwanet al,2019).

In summary NMR might have evolved age combating adaptations, such as telomere elongation in blood, by up-regulating telomerase. While Spalax, telomeres have deteriorated due to the rough environment although they both belong to relatively same species .

When humans were studied, the high variability of T/S values throughout the age range showed that the rate of telomere shortening is likely to vary among different individuals of the same age group(Kim et al,2012).

1.2 Telomere protection and functioning of SIRT1

Many proteins are involved in telomere maintenance like the telomerase complex in proliferating cells and capping proteins that get involved in protection of chromosome termini and help prevent excessive shortening as Dysfunctional telomeres might cause double-strand break (DSB) repair that can lead to genomic instability (Lamarche et al,2010). Moreover,Unlike germ cells and stem cells, terminally differentiated somatic cells lack telomerase activity .The SIRT1 plays a protective role of the minor variant for telomere length and is associated with longevity. XRCC6 is another protein, although important in telomere maintenance, was not linked to longevity in any manner.
SNP in telomerase RNA component gene, TERC and A variant in the 3'UTR of the oligonucleotide/oligosaccharide-binding folds containing 1 gene, OBFC1, whose encoded protein is involved telomere maintenance, were also associated with longevity(Kim et al,2012).

Alternative forms of protein capping for maintaining telomere length include homologous recombination (HR) or non-homologous end joining (NHEJ).The NHEJ includes the Ku heterodimer and DNA ligase complex, which help in fusing DNA ends without the substantial homology . "In normal cells with intact telomeres, Ku promotes genomic stability by repressing intra- or inter-

chromatid exchange via the telomeric repeats .It also interacts with hTERT, the catalytic subunit of telomerase reverse transcriptase and SIRT1, as shown by co-immunoprecipitation ”(Kim et al.2012).

The Sirt1 is essential for the repair via HR in the DSB's SIRT1, and also in DNA repair in its catically inactive form along with ku70 A catalytically inactive form of SIRT1 undermines deacetylation of Ku70 and its role in DNA repair thus maintaining telomere integrityIncreased expression of SIRT1 in mice results in longer telomeres(Kim et al ,2012).

There was a study in telomeres of caucasians to understand the role of SIRT1 better.
The T/S ratio was considered and related to SNPs(Single Nucleotide Polymorphism).Since the SIRT1 had shown positive correlation with endophenotype of telomere length,the next step taken was testing for longevity association.For this the allele and genotype frequencies of rs7896005 in Caucasian (European-origin) subjects of the LHAS(Louisiana Healthy Aging Study) were considered.The frequency of the minor allele of the SIRT1 SNP rs7896005 was higher in the long-lived cases (≥90 years old) than in the young controls (20–59 years old) of the LHAS. Thus there was similarity seen between this recessive model and the model for association with telomere length(Thomas p et al ,2002).

While this study gives the evidence of the association of SIRT1, it is also possible that there is no link between telomere attrition and lifespan and the connection of SIRT1 and longevity depends on other factors that dont concur with telomeres . For instance increased sirtuin activity helps lower aging-related metabolic dysfunction and cancer risk. While sirtuins 1, 2, 6 and 7 operate in the nucleus, sirtuin 3, 4 and 5 are located in mitochondria and affect mitochondrial proteins.Some studies found this association while some contradict it saying genetic variation in SIRT1 has no association with longevity but variants in SIRT2,3,4,5,6,7 show associations with longevity(Kim et al, 2012).

In Conclusion,studying telomere dynamics in long-lived organisms and centenarians is of particular importance since they may have developed mechanisms that actively postpone senescence and promote effective defenses against the deteriorating effects of aging processes.

2.DNA Methylation and mutation

DNA methylation data have been used as biomarkers of aging ("epigenetic clocks"), enabling accurate age estimates for any tissue across the lifespan(Brian et al,2018).

It is hypothesized that suppressing disease-related genes in longevity individuals is likely achieved by epigenetic modification, e.g. DNA methylation.These methylation patterns are distinct to different human immuno- systems during hematopoiesis (Fu-Hui Xiao et al,2015).
With aging, chromatin modifications show increase in heterogeneity between individuals and elevation in cell-to-cell variability.

According to a mitochondrial theory of aging , senescent cellular changes are related to the balance between inherited healthy mitochondrial DNA and the load of age-related mutations in this DNA. Incase of damage of these DNA , the regeneration of new mitochondria is prevented which causes a reduction in adenosine triphosphate and leads to cell death.(Brian et al,2018).

2.1 How does it affect aging ?

The aging cell is exposed to ROS(Reactive Oxygen Species) that can increase inflammation, induce DNA damage and influence DNA methyltransferase (DMT) activity. The damage results in an increase

in mutation frequency and affects the DNA methylation of nearby cytosine bases. Hydroxylation of guanine (to yield 8-hydroxy-guanine) causes a >90% decrease in methylation of neighboring cytosine .It was suggested that this process may help to explain the age-related drift in hypomethylation.(Fu-Hui Xiao et al,2015)

DNA methylation, of methyl group to the 5-position of cytosine (5m-C), contributes in regulating gene expression(Fu-Hui Xiao et al,2015).

It has been observed that with aging a reduction of genome-wide DNA methylation level and locus-specific hyper-methylation occurs , changes in DNA methylation were reported to be associated with the occurrences of age-related diseases, such as cardiovascular disease, diabetes and cancer. When,(Fu-Hui Xiao et al,2015) observed DMRs(DNA methylated regions) in the study of chinese women , it was likely that they have functional roles in regulating disease-associated gene expressions, with some genes [e.g. caspase 3 (CASP3)] being down-regulated whereas the others [i.e. interleukin 1 receptor, type 2 (IL1R2)] up-regulated. Therefore, suppressing the disease-related genes via epigenetic modification is an important contributor to human longevity(Fu-Hui Xiao et al,2015).

2.2 SNP

Genetic variation is caused by mutations—a deletion, insertion, or substitution—in a single nucleotide in a DNA molecule,this is termed single nucleotide polymorphisms (SNPs). Exonic SNPs usually affect protein structure or function SNPs in intervening non coding sequencing (introns) which may alter phenotype (Warren et al,2004).

2.3. Histone
Methylation of the histone octamer has been found to be most important concerning the gene expression .The transcriptional activity is affected by chromatin structure change and or enzymes(Brian et al,2018).

With the help of histone acetylation/methylation,transcription of genes can be either activated (H3K4me3) or repressed(H3K27me3) thus changing chromatin state with aging.
When this phenomena was tested in C.elegans ,it was found that aging these organisms results in a global decrease in somatic H3K27me3.While on their increase, lifespan was extended , but this was applicable only on this organism.

In aging, there is a general loss and disorganization of histones that is assumed to lead to the dysregulation of underlying genes. Evidence for this is an abnormal phasing of histones and induction of repressed genes in yeast

Global H3K27me3 levels increase with age in some organisms, while they decrease with age in others thus identifying the locus- and cell-type-specific dynamics will be critical to obtain a better understanding of factors that influence lifespan.Histone modifications also modulate CDKN2A and TERT expression, affecting aging(Brian et al, 2018).

2.4 caloric restrictions(CR)

Caloric restriction retards the aging process by inducing changes in gene expression of a relatively few genes that cause a metabolic shift toward increased protein turnover and decreased macromolecular damage.In Most Mammals, the Cpg (regulate gene expression through transcriptional silencing of the corresponding gene.)sites near the transcription start sites of genes

tend to methylate during healthy aging and can be used as biomarkers of epigenetic age(Brian et al,2018).

In humans, rhesus monkeys, CR delays age related methylation resulting in younger "methylation age". Thus this methylation drift is another great serving biomarker of aging as it is a mediator of age related functional decline and diseases.In addition to this the hypomethylation of highly expressed genes for liver function in ad libitum fed mice was suppressed in CR while hypermethylation was enriched at the cpg islands .

Genome-wide methylation profiling in nonagenarians identified 19 mortality-associated CpG sites that correlated with the genes whose function were clustered around the nuclear factor KB complex, indicating an important role for this complex in human longevity .

Recent studies have found epigenetic diets that include components such as green tea, broccoli sprouts and soybeans.Consumption of such diets may lead to alteration of chromatin profiles,that also occur in CR - slowing aging and reducing risk of degenerative diseases with age and so, global gene expression profiling methods have been developed to identify CR mimetics that are able to delay aging (Brian et al,2018).

2.5. Non coding RNA

Noncoding RNAs may provide some of the missing links in the aging process .A progressive change in expression of 69 non-coding RNAs (56 microRNAs and 13 snoRNAs) is seen with chronological age (Brian et al,2018).

5 miRNAs targeted 24 aging-associated mRNAs which included PARP1, IGF1R and IGF2R mRNAs. While lncRNAs are evolutionary and species specific yet, a list of lncRNAs involved in regulation of cellular senescence and aging has been compiled. eg:ANRIL.

When RNA's were studied in mice, it was found that the expression of miRNAs, lncRNAs and transposable elements were largely repressed and that the miRNA-targeting sites were enriched for genes having chromatin-related functions.Eg: chromodomain helicase DNA binding protein which is applicable in chromatin remodeling .

Hence,Genetic variants in noncoding RNAs have the potential to differentially influence aging processes and lifespan(Brian et al,2018).

3. Prominent gene influence and allele.

There is a relatively small number of genes which one has to not have in order to survive to extreme ages.

The gene E ɘ-2 allelic is termed as "longevity assurance gene" as its frequency increases with age,however the importance of the reduction of the disease causing ɘ-4 allele must be considered while studying longevity(Thomas et al,2002).

Experiments studied by Jazwinski in yeast, nematode worm *C. elegans*, *Drosophila*, mice have shown 19 genes that determine life span in yeast by implementing four determinants of life span (metabolic control, resistance to stress, gene dysregulation and genetic stability.) and that Specific

mutations in *C. elegans* (daf-2, daf-15, daf-23, age-1, clk-1) increase the nematode's life span by up to three to five times. The mth(Methuselah) mutant strain survived 35%longer than wildtypes in *Drosophila* as this gene is responsible for signal transduction and modulation of stress response.

In these organisms and humans, Overexpression of Cu/Zn superoxide dismutase (SOD) plays a critical role in the scavenging of reactive oxygen species(Thomas et al,2002).

The notable allelic frequencies of the human homologous can be determined in specific human phenotypes such as centenarians, and compared with ethnically matched younger controls .However it is important to note that the gene-gene and gene-environment interactions of a human homologue are likely to be far more complex than such interactions in the lower organisms .

3.1 APOE

The APOE is located in the 20-kb TOMM40 (translocase of outer mitochondrial membrane 40 gene),all genes part of the cluster (TOMM40/APOE/APOC1) are influenced together.

The g-allele of SNP rs2075650 located in the promoter of TOMM40 is responsible for contrasting APOE which contains the e-2, e-3, e-4 genes associated with longevity(Brian et al,2018).

3.2 Insulin growth factor (IGF)and FOXO3

(Warren S.et al,2004)The Variation/mutation in homologs of insulin and insulin-like growth factor 1 signaling have extended lifespan up to sixfold in model organisms-mice, fruit flies, and worms.In C. elegans, mutation in daf-2,the homolog of the insulin and IGF-1 receptors, slows tissue aging and doubles lifespan.Dwarf mice with deleted growth hormone receptor(reduction of insulin/IGF-1 signaling pathway), live longer than normal mice .In Drosophila , gene chico, which participates in an IGF signaling pathway extends median life span of the fruit fly by up to 48% in homozygotes and 36% in heterozygotes.(Warren S.et al,2004)

In one study, a SNP in the IGF-1 receptor gene was associated with human longevity, as well as with lower circulating levels of IGF-1.The human homologue of daf-2 is the insulin/insulin-like growth factor (IGF)-1 receptor.There was also an increase in height in a japanese but this was restricted to male.(Homozygotes were 2.5 cm taller and lived 10 years longer.)(Brian et al,2018).

The forkhead/winged helix box group O (FoxO) transcription factors are crucial component(s) of the insulin/insulin-like growth factor (IGF-1) signaling (IIS) pathway.
These components are responsible for the binding of IGF to their respective receptors to help activate the adenosine monophosphate-activated protein kinase (AMPK) which is involved in maintenance of cell metabolism in response to several functions and aging.(Brian et al,2018)

The FOXO proteins regulate several genes involved in factors like energy metabolism and cell cycle Thus dampening the negative effects of the IIS signaling pathway of lifespan.

There have been four FOXO proteins found in mammal cells (FoxO1, FoxO3, FoxO4 and FoxO6). Studying centenarians globally, the SNPs(strongest:rs2802292) of FoxO3 have shown positive correlation with aging (Brian et al,2018).

In german, French and Danish populations,other intronic SNPs were enhanced .There was an allele-specific binding of CCCTC-binding factor (CTCF) and serum response factor (SRF),that lead to increase in the FOXO3 expression of the longevity-associated allele of each in luciferase reporter gene assays.

Studies have found that the transcription factor heat shock factor 1 (HSF1) binds to the enhancer sequence created by the G allele of rs2802292 in FOXO3 intron 2, so ,by resilience to stress, this SNP is associated with longevity(Brian et al,2018).

Thus the evolutionary role of IGF signaling pathways from species to species suggests the importance of investigating such pathways and their relation to aging and longevity in humans.

3.3 Other minor genes

BPIFB4(bactericidal/permeability-increasing fold-containing family member 4 gene,). This gene reduces vasorelaxation and increases diastolic blood pressure by impairing the endothelial nitric oxide synthase activity.
Polymorphism of BPIFB4, by modulating endothelial function and angiogenesis, was associated with longevity by reducing blood pressure and rescuing endothelial dysfunctioning .Serum BPIFB4 protein levels were higher in healthy centenarians, but lower in frail centenarians (Brian et al,2018).

Bcl-xL is involved in mitochondrial damage protection, control of mitochondrial respiration , modulation of the immune response and DNA repair, all of which are associated with healthy aging.BCL2L1 mRNA expression and protein were higher in centenarians . In *c.elegans* there was an increased survival with the active mutant of the *C elegans* BCL2L1 ortholog, ced-9.

Another Gene is the tumor-suppressor p53 gene (TP53) . This reduced expression of these genes in neurons due to the reduced cell-cycle related proteins was found to have a possible effect on the exceptional lifespan of low-turnover cells and tissues such as neurons, heart muscle and skeletal muscle, and perhaps human longevity(Brian et al 2018).

4. Aging diseases

 A landmark study of the health of supercentenarians (aged 110–119), semisupercentenarians (aged 105–109), centenarians (in this context aged 100–104), nonagenarians, and younger controls found that the older the age group, the greater was the delay in onset of major disease .In the study,the identified DMRs were significantly enhanced with genes linked to diseases like   type-2 diabetes, stroke,cardiovascular disease and Alzheimer's disease(Andersen et al. 2012).

Upon further examinations of expression patterns of the genes containing DMRs, the Alzheimer's disease-associated gene CASP3 shows high expression in the patients, which however has a hypermethylated DMR near its transcription start site in centenarians. Similarly, IL1R2 gene has a lower expression in atherosclerotic disease but contains a hypo-DMR near its transcription start site in our centenarians.(Thomas.et al,2002)

Another meta -analysis with Caucasians, of multiple mitochondrial DNA showed association of their haplogroups, type 2 diabetes, dementia and cancer on longevity.As centenarians have a relatively high mitochondrial copy number it was likely mediated by single-stranded DNA-binding protein 4 and was significantly associated with DNA copy number resulting in adequate maintenance of energy supply.

The effect of FOXO3 risk alleles on cardiovascular disease earlier in life might help explain an apparent association with vascular factors and Alzheimer's disease (Brian et al,2018).

It is evident that centenarians and supercentenarians somehow manage to escape these diseases and thus live longer.

4.1 Progeroid syndrome-

This is another approach to discovering genes in humans that play roles in aging and possibly longevity.

Werner's syndrome (WS), the most popular , is a rare autosomal recessive disorder that mimics premature aging .It includes development of cataracts at a young age, aged skin, and cardiovascular disease.WS patients presumably age more quickly because they accumulate DNA damage faster than normal(Thomas P.et al,2002).

5.Centenarian features,heredity and demographic impact

Centenarians may be a human model of disease-free or, at the least, disease-delayed aging. A number of studies have been performed to search for factors that could play a role in such a survival advantage.such as that of body fat and metabolism, pedigree studies,and cardiovascular risk factors.etc..In a study conducted, there was a mass increase in the RSP(Relative Survival Probability)levels in centenarians making it evident that they have unique features.Many members of the elderly and centenarian cohorts under study today lived through times of caloric restriction (e.gThe Great Depression)(Thomas P.et al,2002).

 Investigations by De Benedictis et al. noted that specific mitochondrial haplotypes significantly varied in frequency between centenarians and younger controls(Thomas P.et al,2002).

Eg:-oxidative stress. A comparison done by (Paolisso et al) among three age groups, healthy young, older, and centenarian subjects, for indices of oxidative stress, centenarians resulted in a lower degree of oxidative stress compared to the older subjects.

Healthy Canadians aged 85 years found reduced prevalence of the APOE ε4 allele in comparison with random midlife controls same was with the japanese centenarians. Scientists based on these results speculate that these individuals have genetic factors that confer resistance to such diseases and increase the likelihood of reaching exceptional old age and that it may also be hereditary(Brian et al,2018).

5.1 Heredity.
Several studies have demonstrated heritability of longevity over age 60 like the population-based study of 2,872 Danish twin pairs (1870-1900) which found that the heritability of adult lifespan was 0.26 in men and 0.23 in women (Herskind et al. 1996).Exceptional familial clusters of extreme longevity have also been reported .

Nir Barzilai et al., studying Ashkenazi Jewish centenarians, noted that the presence of Lipid profiles reduced the exposure to cardiovascular diseases.The same factors when explored in their children showed that they also had favorable profiles,thus suggesting the involvement of some familial component(heredity).

There was a genome wide scan of The survival of siblings of 102 centenarians when compared with the survival of siblings of a control group who were from a similar birth cohort but of parents who died earlier showed that survival steadily increased with age for siblings of the centenarians to the point that they had four times the probability of surviving to age 91.Following this was another

study among Mormon pedigrees from the Utah Population Database by (Cawthon et al). This study led to a possible hypothesis that there exists a substantial Mendelian genetic component to exceptional longevity that supports the conduct of molecular genetic studies to locate longevity enabling genetic loci among sibling pairs(Thomas P.et al,2002).

Thus Studying families can help understand the connection between a trait and a chromosomal region, it will also help understand the connection of a particular gene or polymorphism thus detect the joint effects of two or more genes (Warren et al.2004).

5.2 Demography and gender

One piece of evidence for a role played on the longevity trait by population-specific genetic factors is given by the observation that the male/female (M/F) ratio in centenarians differs among countries whose populations have different gene pools.For eg: the M/F ratio increases from northern to southern Europe; it varies from 1:4 to 1:7 in northern European countries this variation is possibly due to geographic isolation and endogamy (inbreeding)(Giovanna et al,2006).

In a parallel study conducted between the italian and danish, there was a correlation of short allele with longevity in italian but not in danish centenarians . These contrasting results could be explained by different gene pools (Giovanna et al,2006).

Women have higher mortality rates and genetic composition that favor their longevity when compared to men ,female hormones like estrogen facilitate the elimination of bad cholesterol and thus may offer some protection against heart disease(Bertrand,2004).

The role of women in reproduction has also been linked to greater longevity. Women who naturally had a child in their forties had a four times greater chance of living to 100 than did those women who had children at younger than age 40.Such slow aging and the avoidance or delay of diseases that adversely affect reproduction would bode well for the woman's subsequent ability to achieve very old age(Thomas et al,2004).

Further men have higher exposure to what we call man made diseases and behaviors that prevent them from long age.(Bertrand.2004)

RESULTS:

Clinical trials and future expectations-

Clearly aging is plastic and can be substantially retarded in animal models via genetic manipulations, diet, and drugs.studies in mice, flies and worms have questioned the assumption that lifespan extension is always accompanied by an increase in healthspan
Impressively, single gene manipulations can extend longevity by as much as 50% in rodents and up to tenfold in invertebrates but what about humans?

Humans with extreme longevity presumably have favorable aging mechanisms delaying the onset of most major chronic diseases(João Pedro,2021).

There's a lot of research being done to progress to clinical trials of humans with longevity drugs but how effective are they?

Drug developers focus mainly on the proteins and internal processes (oxidative stress,length of telomere…) of model organisms.An emphasis is also laid on dietary or caloric restrictions. However, One limitation of longevity experiments in animal models is that they often use strains of limited genetic diversity, which might not always translate to clinical applications in the much more diverse human population(João Pedro,2021).

Nowadays,there is a greater focus in translating results from the basic biology of aging to the clinic. Pharmacological approaches are the primary means by which clinical translation can be achieved which is why there is sudden growth in the number of longevity drugs discovered in model organisms.

Companies like Calico, a Google-backed biotech, are now investing and funding longevity biotechnology(João Pedro,2021).

Few pathways like the target of rapamycin (TOR) have been suggested as mediators of the actions of dietary restrictions, thus, are exciting pharmacological targets in the context of longevity .This also led to the discovery in 2009 that mice fed rapamycin late in life lived longer , another clinical study in Novartis showed that low-dose mammalian TOR (mTOR) inhibition improved immune function and reduced infections thus creating a spotlight on rapamycin.

Other trials include- Alkahest ,targeting chronokines, proteins that increase or decrease with age, with several clinical trials for neurodegenerative diseases.

BioAge, a company using data-driven approaches to identify drug targets for treating aging diseases, conducted a Phase II trial for COVID19 using an inhibitor of prostaglandin D2 and Targeting Aging with Metformin (TAME) clinical trial, which hoped to serve as a proof of concept for a US Food and Drug Administration (FDA) clinical trial focused on aging.

The multicentre Intervention Testing Program (ITP), which is supported by the National Institute for Ageing,has identified a few notable drugs.At least five major classes of drugs are currently being tested in humans for their geroprotective potential(João Pedro,2021).

1. Rapamycin(sirolimus) and its analogue everolimus

Studies have proven a relationship between TOR(a versatile protein that integrates signals from growth factors, nutrient availability, energy status and various stressors)and dietary restriction. When this was tested in flies,mice yeast etc..it showed positive response thus aiming for clinical trials.

In a clinical trial with healthy older adults who were given a non-immunosuppressive dose of everolimus for six weeks there was a improved immunological response to influenza vaccination .Another one found that six weeks of low-dose everolimus plus a second TOR inhibitor improved vaccine response , reduced infection rates during the subsequent nine months(Campisi et al, 2019) .

2. .Metmorfin

A widely prescribed antidiabetic drug that targets several molecular mechanisms of aging. In random trials,metformin prevented the onset of diabetes, improved cardiovascular risk factors and reduced mortality.epidemiologists suggest that this drug may reduce the incidence of cancer and neurodegenerative diseases(Campisi et al, 2019).

Drugs like Senolytics, NAD+,precursors and Sirtuin activators are also being explored but thus far there has not been any positive response to clinical trials(Campisi et al ,2019).

There are also other mechanisms being prioritized (eg:AI-)given that the drugs may have adverse effects. One promising area involves drug repositioning(the discovery of new clinical indications for existing drugs for which some information is known)(João Pedro,2021).

Future Studies and Conclusions

While the knowledge of the public remains constricted to the association of longevity to external factors, such as the environment, individual diet, behavior, and exercise, this analysis focuses on the contribution of intrinsic factors, such as telomere shortening, DNA methylation, the presence of specific alleles, insulin growth factors, and other internal mechanisms that can contribute to healthy aging.

These factors serve as biomarkers for aging and are important to understand before approaching clinical trials in humans for drug creation that may help extend lifespan .
To date there has been lots of research in this field, I presume that there is scope for creation of effective drugs in the next couple of years with the advancement of current technology.
However,scientists may come across some challenges while developing longevity drugs for people living in different geographical locations and having different phenotypes.

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