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Original Article

Mosaic Chromosomal Alterations and Human Longevity

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Abstract

Mosaic chromosomal alterations (mCAs) are structural alterations associated with aging, cancer, cardiovascular disease, infectious diseases, and mortality. The distribution of mCAs in centenarians and individuals with familial longevity is poorly understood. We used MOsaic CHromosomal Alteration (MoChA) to discover mCAs in 2050 centenarians, offspring, and 248 controls from the New England Centenarian Study (NECS) and in 3 642 subjects with familial longevity and 920 spousal controls from the Long-Life Family Study (LLFS). We analyzed study-specific associations of somatic mCAs with age, familial longevity, the incidence of age-related diseases, and mortality and aggregated the results by meta-analysis. We show that the accumulation of mCAs > 100 KB increased to 102 years and plateaued at older ages. Centenarians and offspring accumulated fewer autosomal mCAs compared with controls (relative risk 0.637, $p = .0147$). Subjects with the APOE E4 allele had a 35.3% higher risk of accumulating autosomal mCAs ($p = .002$). Males were at higher risk for mCAs compared to females (male relative risk 1.36, $p = 5.15e{-}05$). mCAs were associated with increased hazard for cancer (hazard ratio 1.2) and dementia (hazard ratio 1.259) at a 10% false discovery rate. We observed a borderline significant association between mCAs and risk for mortality (hazard ratio 1.07, $p = .0605$). Our results show that the prevalence of individuals with mCAs does not continue to increase at ages >102 years and factors promoting familial longevity appear to confer protections from mCAs. These results suggest that limited mCA accumulation could be an important mechanism for extreme human longevity that needs to be investigated.

Keywords: Aging, Clonal hematopoiesis, Mosaicism

Mosaic chromosomal alterations (mCAs) detected from blood-derived DNA genotypes are structural somatic alterations (deletion, duplication, and copy neutral loss of heterozygosity) that correlate with older age, and increased risk for mortality, hematological malignancy, cardiovascular diseases, diabetes, Alzheimer's disease, as well as predisposition to various infectious diseases (1–21). Large mCAs may introduce significant functional disruptions because they affect a substantial number of genes that are involved in multiple functions. Therefore, mCAs can greatly contribute to risk of disease progression and aging-related disease progression. It has been suggested that the rate of mCAs, like the rate of the somatic mutations, should continue to increase exponentially in people who reach the extreme of human lifespan (1,21). However, centenarians, that is, people who survive past the age of 100 years, and their offspring can delay the onset of aging-related diseases and compress morbidity and disability until the very end of their long lives (22–25). Furthermore, the exceptional phenotypic features shared among the centenarians and their offspring suggest that these individuals are enriched for genetic and molecular factors that promote healthy aging and provide survival advantages. In this manuscript, we test the hypothesis that centenarians have a reduced accumulation of mCAs that contributes to their extended lifespan.

To date, the distribution of mCAs in centenarians and their offspring has not well described. Analyses of large population-based cohorts included mostly middle-aged individuals with a small proportion of centenarians (UK BioBank—mean

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age of the subjects is 57 [standard deviation {*SD*} = 8 years], Mass General Brigham Biobank [MGBB]—mean age of 55 [*SD* = 17], FinnGen—mean age of 53 [*SD* = 18], BioBank Japan—mean age of 65 [*SD* =12]) (1,14,21). We analyze mCAs in blood samples from centenarians, their siblings, and offspring from the New England Centenarian Study (NECS) (22), and individuals with familial longevity from the Long-Life Family Study (LLFS) (26) to characterize the distribution of mCAs at extreme old ages and their relations to healthy aging.

Methods

Study Population

Data from the Long-Life Family Study (LLFS) and the New England Centenarian Study (NECS) data were available for analysis.

Data

New England Centenarian Study (NECS)

The NECS data set included 2 298 participants enrolled between 1995 and 2018. Participants comprised centenarians, their siblings, their offspring, and unrelated controls without familial longevity (22). Study participants provided detailed demographic information and self-reported medical history at enrollment, as well as measures of cognitive and physical functions. Participants are followed up annually to update medical events, and the cognitive and physical functions. Blood DNA samples were genotyped with Illumina SNPs arrays (370k and 610k SNPs) and then augmented with additional genome-wide genetic controls provided by Illumina. We created the variable "longevity-related" to label the data of centenarians and all participants genetically related to them as one group versus the "control" group that comprised offspring spouses and controls without familial longevity. Written informed consent was provided by all study participants and the study protocols were approved by the Institutional Review Boards at Boston University.

The Long-Life Family Study (LLFS)

The LLFS enrolled ~ 5 000 participants from long-lived families at the three field centers in the United States (Boston, Pittsburgh, and New York), and a field center in Denmark between 2006 and 2009 (26). Self-reported medical history, socio-demographic, current medical conditions and medications, physical and cognitive decline data were collected via in-person and annual phone interviews, and updated through annual follow-ups (27). The study generated genome-wide genotype data (~2.5 m SNPs) for 4 562 subjects using an Illumina SNP array, and are available from dbGaP (dbGaP Study Accession: phs000397.v1.p1). Similarly to the NECS data, we created the "longevity-related" variable to label subjects with familial longevity as one group versus the "control" group that comprised offspring spouses and controls without familial longevity. Written informed consent was provided by all study participants and the study protocols were approved by the Institutional Review Boards at Boston University and the other participating institutions of the LLFS including Columbia University, University of Pittsburgh, University of Southern Denmark, and Washington University in St. Louis.

In both studies, current smokers were defined as subjects who smoke cigarettes, pipes, and cigars on a regular basis. A regular drinker was defined as a subject who has at least one alcoholic drink a week.

mCA Detection

Mosaic Chromosomal Alterations (MoChA) software and pipeline (https://github.com/freeseek/mocha) were used to detect mosaic chromosomal alterations (1). MoChA utilizes a Hidden Markov Model to detect mCA-induced deviations in allelic balance at heterozygous sites with Log R Ratio and B-allele frequency (BAF) with phased genotype information. We used the recommended pipeline parameters, analyzing somatic mCAs over 100 kbp with an estimated cell fraction less than 50%, with genome-wide BAF phase concordance across phased heterozygous sites less than 0.51, and with a logarithm of the odds (lod_baf_phase) score of more than 10 for the model based on BAF and genotype phase, which removed calls flagged as germline copy number polymorphisms, and the calls that are likely germline. Autosomes and chromosome X (for NECS only) were analyzed separately.

Statistical Analysis

We computed the number of the detected mCA "mCA_count" within a sample and used this variable as either the outcome or the predictor variable in the analysis. Specifically, to estimate the effect of familial longevity (Cohort: "longevity-related" and "control") on mCA_count, we fit the Poisson regression using the "*glm*" R package:

$$\text{mCA\_count} = \text{Cohort} + \text{Sex} + \text{Age at enrollment} + \text{Age at enrollment}^2$$

We used a similar Poisson regression model to estimate the effect of *APOE* alleles on mCA accumulation, adjusting for sex, and age at enrollment:

$$\text{mCA\_count} = \text{APOE} + \text{SEX} + \text{Age at enrollment}$$

APOE alleles E2, E3, and E4 were defined based on genotypes as E2= e2e2 or e2e3; E4: e3e4 or e4e4; and E3: e3e3. The alleles e2, e3 and e4 were based on combination of the SNPs rs7412 and rs429538 as follows: e2: rs7412 = T and rs429538 =T ; e3: rs7412 = C and rs429538 = T; e4: rs7412 = C and rs429538 = C. In LLFS, we estimated coefficients using generalized estimating equations ("*geeglm*" R package) to adjust for the within family correlation.

To evaluate the effect of mCA on mortality, adjusting for sex and age at enrollment, we used Cox Proportional Hazard regression using the coxph() function in the R package "surv" and used Schoenfeld residuals to check the Proportional Hazard assumption. We stratified the analyses by secular trend using the *strata()* option to define different baseline hazard functions for each age at enrollment decade. To take into account the family effect on mortality in LLFS data, we used the *cluster()* function in the model. The specific regression model was:

$$\text{coxph}(\text{surv}(\text{Last contact age}, \text{Status}) = \text{mCA\_count} + \text{strata}(\text{Age at enrollment range}) + \text{Sex}, \text{cluster} = \text{Family});$$

where Status indicates a deceased status.

To evaluate the association of number of mCA in a sample and incident events, after the enrollment, we used Cox

Proportional Hazard regression with the same adjustment used for survival analysis described earlier:

$$\begin{aligned} &\text{coxph}\,(\text{surv}\,(\text{Last contact age},\ \text{Status}) \\ =\ &\text{mCA\_count} + \text{strata}\,(\text{Age at enrollment range}) \\ &+ \text{Sex},\ \text{cluster} = \text{Family})\,; \end{aligned}$$

where Status indicates the occurrence of the incident event.

We conducted fixed-effect meta-analysis was performed using the R package "*rmeta*" with the function *meta.summaries()* and the parameter *method="fixed*."

Results

Table 1 summarizes the main characteristics of the 2 298 participants from the NECS, and the 4 562 subjects from the LLFS. The mean age at enrollment in NECS was 92.0 years (*SD* 15.2 years), and the mean age at enrollment in LLFS was 70.3 years (*SD* 15.7 years). Only 32% of the NECS subjects were males, although 45% of LLFS subjects were males. Most of the participants were white in both studies. The prevalence of participants who consumed alcohol regularly was 9.4% in NECS and 8% in LLFS. The prevalence of current smokers at enrollment was 0.3% in NECS and 7.3% in LLFS. The NECS cohort included 10.8% controls, although the LLFS included 20.2% controls with no familial longevity.

We applied the MoChA pipeline to detect mCAs in NECS and LLFS from genome-wide genotyping of blood DNA. For subsequent analyses, we selected 780 somatic mCAs (368 in NECS and 412 in LLFS) spanning over 100 Kbase pairs, using the quality control steps described in the methods (Figure 1A and B). In NECS, 10.8% of the subjects had at least one mCA at enrollment, and 9.25% of subjects had at least one autosomal mCA, and 2.61% carried an alteration in the X chromosome (Table 1). In LLFS, 7.04% of the subjects had at least one autosomal mCA at enrollment. The majority of detected mCAs in NECS were deletions and duplications (46% deletion, 28% duplication, 23% copy-neutral loss of heterozygosity, and 3% undetermined). In LLFS participants, duplications and copy-neutral loss of heterozygosity were more prevalent (37% duplication, 33% copy-neutral loss of heterozygosity, 29% deletion, and 1% undetermined).

Figure 1 describes the prevalence of subjects with at least one detected somatic mCA for increasing ages in NECS and LLFS. Panel 1A shows an increase in the prevalence of NECS subjects with mCA up to age 102 years but, after age 102, the proportion of NECS subjects with mCA dropped. Panel 1B shows a similar pattern in LLFS participants up to age 102 but the number of LLFS participants aged >102 years was too small ($n = 14$) to detect any reliable trend. In addition, the plots show that a smaller portion of longevity-related individuals in NECS carried mCA compared to controls in all age groups.

We next employed regression analysis to quantify the effect of familial longevity and age on the risk for mCAs. The results of the analysis are summarized in Table 2 and show that NECS centenarians, centenarians' siblings, and offspring accumulated significantly less autosomal mCA compared to controls (Table 2: relative risk 0.45, $p = .002$) although there was no significant difference in the proportion of subjects with mCA detected in chromosome X (Supplementary Table 3A). In LLFS, members of long-lived families also accumulated fewer mCAs than controls (Figure 1B), although the difference was not statistically significant (Table 2: relative risk 0.90, $p = .5831$). Meta-analysis of the study-specific results showed that longevity-related subjects had a statistically significant reduced risk of carrying an mCA compared to controls (Table 2: relative risk 0.64, $p = .0147$). Interestingly, in NECS, we adjusted the analysis by a statistically significant quadratic trend with age that was consistent with the plateauing of

Table 1. Summary Statistics of the MoChA Input and Output Data

	NECS	LLFS
Samples	2 298	4 562
Age at enrollment range	39–119	24–110
Mean age at enrollment	91.98 (*SD* = 15.24)	70.32 (*SD* = 15.71)
Male/female samples	747/1 551	2 065/2 497
Race	White—98%	White—99.9%
Regular alcohol drinker	9.40%	8%
Current smoker	0.30%	7.25%
Longevity-related/control samples	2050/248	3642/920
Subjects with mCA	10.80%	7.04%
Number of centenarians (age 100 and above)	1 129	60
Type of mCA (% from all detected mCAs)		
Deletion	46%	29%
Duplication	28%	37%
CN-OH	23%	33%
Undetermined	3%	1%
Subjects with autosomal mCA	9.25%	7.04%
Subjects with X mCA	2.61%	

Notes: CN-OH = copy neutral loss of heterozygosity; LLFS = Long-Life Family Study; mCA = mosaic chromosomal alteration; NECS = New England Centenarian Study; *SD* = standard deviation.

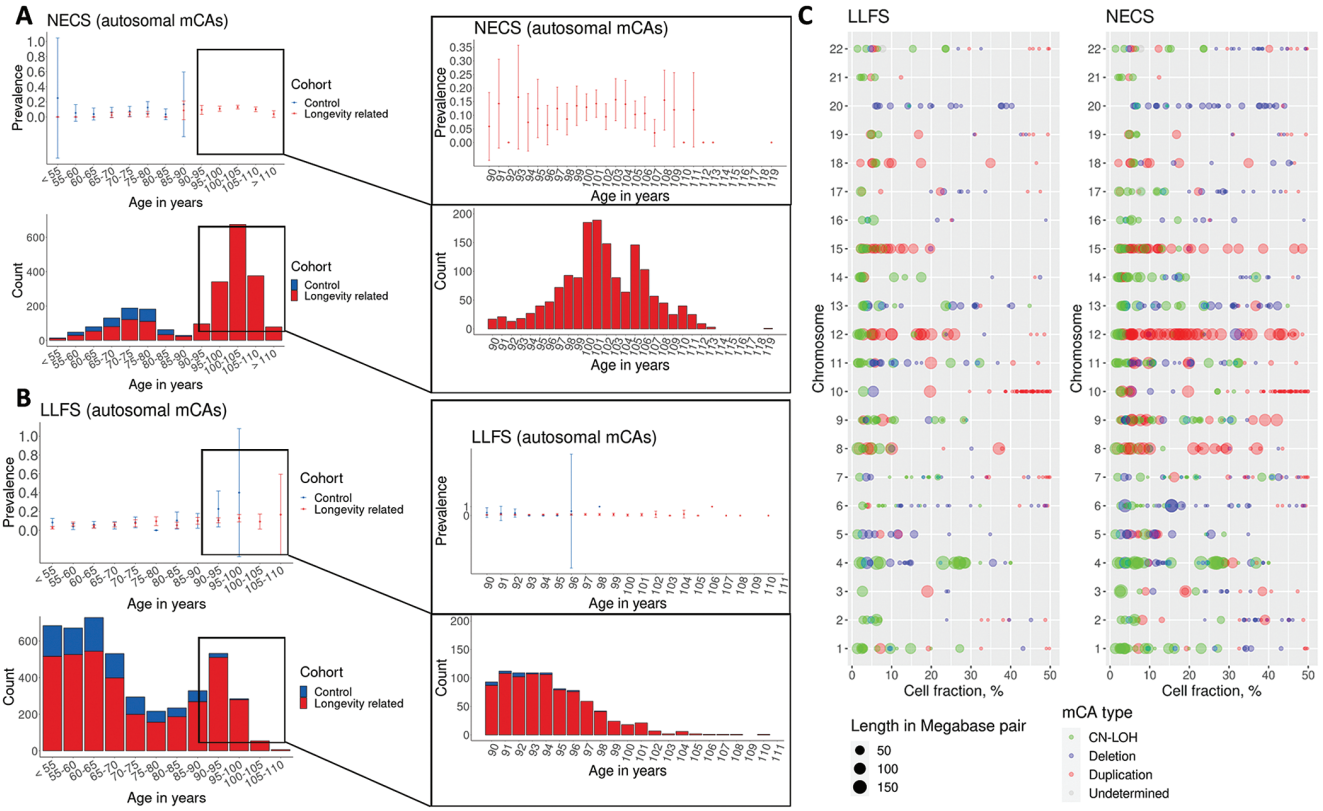

Figure 1. The detected autosomal mCA in the NECS and the LLFS data sets. (A) The prevalence of subjects with the detected autosomal mCA over age ranges for longevity-related cohort (red) and controls (blue) in NECS (upper panel) and frequency of the enrolled subjects over age ranges (lower panel). The graph demonstrates an increase in the proportion of subjects with mCA in the longevity-related cohort with age up till 102 years and then plateaus at older ages suggesting that mCAs are incompatible with extreme human longevity. (B) Prevalence of subjects with autosomal mCA over age ranges for longevity-related cohort (red) and controls (blue) in LLFS (upper panel) and frequency of the enrolled subjects over different age ranges (lower panel). The plot demonstrates a steady increase in the proportion of subjects with autosomal mCA in longevity-related cohort in LLFS with age. The lack of subjects aged 105 and older in LLFS does not allow to confirm the trend discovered in NECS. (C) The detected mCAs in NECS and LLFS. The detected mCAs (shown as dots) plotted by the location on the genome over the estimated cell fraction in the samples. The size of a dot reflects the size of mCA in Mega base pairs, and the color/shades of grey illustrates the predicted mCA type: on the left—in the LLFS data, on the right—in the NECS data. CN-OH = Copy Neutral loss of heterozygosity; LLFS = Long-Life Family Study; mCA = mosaic chromosomal alteration; NECS = New England Centenarian Study.

mCA accumulation at the extreme old ages (Supplementary Table 2A). In LLFS, we only found a statistically significant linear effect of age (Supplementary Table 2B). The analysis showed that male subjects had an increased risk of carrying an mCA in both NECS (Table 2: risk ratio 1.3, p = .0387) and LLFS (Table 2: risk ratio 1.43, p = .0048). The data in Supplementary Figure 1A also suggests that the increased risk for mCAs persists at different ages for males (Supplementary Figure 1A). The results in the two studies were very similar and were reinforced by aggregating the results in a meta-analysis (Table 2: risk ratio 1.36, p = 5.15e−05).

We next examined how the occurrence of mCA affected the risk for mortality, and for some common aging-related diseases in NECS and LLFS participants (Table 3). In both NECS and LLFS, the presence of at least one somatic mCA was associated with a 6%-7% increased hazard for mortality, although the study-specific results did not reach statistical significance. When we aggregated the study-specific results by meta-analysis the increased hazard ratio was borderline significant (hazard ratio 1.07, p = .0605). Only the association between mCAs and the hazard of cancer reached nominal statistical significance in LLFS (Table 3: hazard ratio 1.22, p = .04). Meta-analysis of all the results showed that mCA increased the hazard for cancer by 20.4% and for dementia by 25.9% at a 10% false discovery rate (FDR).

Given the important effect of the *APOE* gene on survival and other aging-related diseases, we also correlated the *APOE* alleles E2, E3, and E4 with the prevalence of mCA, after adjusting for sex and age at enrollment (25,28). The analysis showed that carriers of the *APOE* E4 allele had a 41.6% higher risk of accumulation of autosomal mCAs (p = .027) compared to E3 carriers in NECS (Table 4). Carriers of the *APOE* E2 allele had 10.9% less risk of accumulation of an autosomal mCA in NECS, although the associations were not statistically significant (Table 4). The results of the analysis performed with all detected mCA types (autosomal and chromosome X) in the NECS data set are demonstrated in the Supplementary Table 3B (Supplementary Figure 3B). In LLFS data, carriers of the *APOE* E4 allele had a 37% increased risk of autosomal mCA accumulation (p = .111), and subjects with *APOE* E2 had a 35% higher risk of autosomal mCA accumulation (p = .084). Only the association between the APOE E4 allele and mCAs became stronger with the meta-analysis and E4 carriers had a 40% higher risk of getting autosomal mCA compared to E3 carriers (p = .0065).

In both NECS and LLFS we did not find a significant association between somatic mCA accumulation and current smoking and drinking statuses (Supplementary Table 1A).

Table 2. The Risk Ratio for mCA (Longevity-Related Subjects* in NECS and LLFS Compared With Controls Without Familial Longevity and Male Subjects Compared With Female Subjects in NECS and LLFS)

Study	Subject Cohort/Label	mCA Type	RR	*SE*	*p* Value	Meta-Analysis RR (NECS and LLFS)	Meta-Analysis *SE* (NECS and LLFS)	Meta-Analysis *p* value (NECS and LLFS)
NECS	Longevity-related	autosomal	0.45	0.261	.0024	0.64	0.185	0.0147
LLFS	Longevity-related	autosomal	0.9	0.199	.5831			
NECS	Male	autosomal	1.3	0.125	.0387	1.36	0.0885	0.00052
LLFS	Male	autosomal	1.43	0.1265	.0048			

Notes: Longevity-related subjects in NECS are centenarians' siblings and offspring. In LLFS, longevity-related subjects are members of family selected for longevity. LLFS = Long-Life Family Study; mCA = mosaic chromosomal alteration; NECS = New England Centenarian Study; RR = relative risk; *SE* = standard error.

Discussion

We used state-of-the-art methods implemented in MoChA (1) to discover mCAs in blood-derived genome-wide genotype data of NECS and LLFS participants. Both studies are enriched for people with familial longevity and these new data allowed us to examine the distribution and the effect of mCAs at extreme old age, and the effect of familial longevity on the risk of developing mCAs.

Accumulation of mCAs With Extreme Old Age

The most surprising result of our analysis was the observation that the prevalence of individuals with mCAs increases with older age up to approximately 102 years and tends to plateau for ages > 102 years (Figure 1). A previous study of a long-lived individuals from United Kingdom and Japan BioBanks showed a steady accumulation of mCA with older age and an estimate that 35% of individuals aged >90 years carried mCAs (1,14,21). The study by Terao et al. used whole-exome sequence data, which usually produces a higher discovery rate of chromosomal alteration compared with the results obtained using genome-wide genotyping data (21,29). The increase of clonal somatic mutations with older age has been reported in several studies and has led to the hypothesis of the inevitability of the presence of such clones at the extreme of human lifespan (8,9,12,13,20,30,31). However, we believe this is the first study that included a large number of centenarians, with 635 individuals aged >102 years (n = 621 in NECS, n =1 4 in LLFS) and 316 individuals aged > 105 years (n = 312 in NECS and n = 4 in LLFS). Although these results need to be replicated in cohorts of similar exceptionally old individuals, they point to chromosomal alterations being incompatible with extreme human longevity.

Effect of Familial Longevity on mCA Accumulation

We found that centenarians and their relatives accumulate fewer mCAs compared with individuals with no familial longevity (meta-analysis summary risk ratio: 0.64, p = .0147). This result suggests a possible genetic protection to the accumulation of somatic mCAs in some individuals that may be the result of better mechanisms for DNA repairs. Previous studies on the genetic predisposition of clonal hematopoiesis support this assumption (32), although a recent study of clonal hematopoiesis of indeterminate potential in adult twins aged 73 to 94 years failed to confirm a genetic predisposition to accumulation of mCAs (31). The phenomenon of a genetic protection from the accumulation of somatic mCA should be further investigated and could lead to novel healthy-aging therapeutics.

Association With Aging-Related Diseases

Consistent with previous studies, we found that mCA accumulation significantly contributes to mortality and cancer, and is more common among males (1,14,21), although we did not find a significant contribution of mCAs to the incidence of cardiovascular diseases, diabetes, and stroke. This lack of an association could be explained by the exceptional health span of the subjects in the analyzed cohorts and the relative small number of incident cardiovascular diseases, diabetes, and stroke that was experienced in both NECS and LLFS participants. We also did not find the association between drinking and smoking statuses and the mCA occurrence reported

Table 3. mCA Hazard Ratio for Incident Diseases and Mortality in NECS and LLFS (Autosomal mCAs)

Incident Disease Analysis						
Study	**Outcome**	***N* Cases/*N* Total**	**HR (CI 95%)**	***p* Value adjusted**	**Meta-Analysis Estimated HR (CI 95%)**	**Meta-Analysis *p* Value Adjusted**
NECS	CVD	665/2297	1.00 (0.81–1.24)	.976	0.99 (0.86-1.15)	.948
LLFS		478/4558	0.99 (0.81–1.21)	.887		
NECS	Cancer	169/2295	1.14 (0.79–1.63)	.644	1.20 (1.03-1.41)	.101
LLFS		436/4556	1.22 (1.03–1.45)	.04		
NECS	Dementia	58/2295	1.25 (0.79–2.00)	.644	1.26 (1.02-1.55)	.101
LLFS		152/4538	1.26 (1.0–1.58)	.156		
NECS	Depression	78/2293	1.22 (0.69–2.15)	.644	1.01 (0.73-1.41)	.948
LLFS		158/4520	0.92 (0.61–1.38)	.887		
NECS	Diabetes	57/2293	0.65 (0.20–2.13)	.644	1.08 (0.75-1.55)	.9374
LLFS		138/4531	1.14 (0.78–1.67)	.887		
NECS	Stroke	123/2293	1.10 (0.76–1.51)	.644	1.06 (0.86-1.30)	.9374
LLFS		228/4556	1.03 (0.78–1.35)	.887		
NECS	Thyroid	83/2294	0.47 (0.13–1.68)	.644	0.86 (0.56-1.32)	.9374
LLFS		147/4497	0.93 (0.59–1.47)	.887		

Survival analysis						
Study	**Outcome**	***N* Cases/*N* Total**	**HR (CI 95%)**	***p* Value**	**Meta-Analysis Estimated HR (CI 95%)**	**Meta-Analysis *p*-Value**
NECS	Mortality	1 377/2 004	1.07 (0.98–1.17)	.138	1.07 (1.00 - 1.14)	.0605
LLFS		1 446/4 556	1.06 (0.95–1.19)	.31		

Notes: CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; LLFS = Long-Life Family Study; mCA = mosaic chromosomal alteration; NECS = New England Centenarian Study.

Table 4. Autosomal mCA Risk Ratio for APOE Alleles in NECS in LLFS

Study	***N* Cases/Data**	**Allele**	**RR**	**SE**	***p* Value**	**Meta-Analysis Estimated RR (CI 95%)**	**Meta-Analysis *p* Value**
NECS	414/2173	E2	0.89	0.161	.475	1.08 (0.86–1.36)	.521
LLFS	688/4421	E2	1.35	0.175	.084		
NECS	321/2173	E4	1.42	0.157	.027	1.40 (1.10–1.78)	.0065
LLFS	857/4421	E4	1.37	0.195	.111		

Notes: CI = confidence interval; LLFS = Long-Life Family Study; mCA = mosaic chromosomal alteration; NECS = New England Centenarian Study; RR = relative risk; *SE* = standard error.

previously (33). This could be because of the low prevalence of tobacco and alcohol use among study participants.

Effect of APOE

Our analysis showed that carriers of the *APOE* E4 allele accumulated significantly more mCAs in both NECS and LLFS, suggesting that *APOE* may contribute to the mCA development mechanism possibly via a reduced DNA repair mechanisms. In contrast, in NECS, *APOE* E2 allele carriers demonstrated a trend toward reduced risk of mCA accumulation, but the result did not replicate in LLFS. Given that mCA occurrence increases the risk of an incidence of dementia by 26% (Table 3), we hypothesize that there is a connection between *APOE* E4, mCA and Alzheimer's disease. Other studies have found suggestive effect of *APOE* in DNA repair and other epigenetic processes in relation to Alzheimer's disease, and further work in this area is warranted (34). APOE is only one of the genes that are associated with extreme human longevity (35), and it will be interesting to expand this work to other genetic variants and their association with mCAs.

Limitations

Possible limitations of this study are introduced by the size of the genotype arrays. NECS samples were genotyped using a combination of SNP arrays including Illumina 370k, 610k SNPs which are smaller than the SNP arrays used for genotyping the LLFS samples (1.2 m SNPs). However, the cohorts were analyzed separately with the presence of independent controls in both studies, and the effects were summarized with the meta-analysis. The tissue specificity of this analysis introduces another limitation. The genotyping was performed on the blood DNA samples, and mosaic chromosomal alterations in other types of tissues were not examined.

Conclusions

Our analysis shows that contrary to conjectures put forward in other studies, the prevalence of individuals with mCAs

does not continue to increase at ages greater than 102 years. In addition, factors that promote familial longevity appear to confer protections from mCAs and genetic factors that are associated with early mortality may also be involved in accumulation of mCAs. Our analysis was limited to mCAs that can be detected using genome-wide genotype data and needs to be replicated and expanded to include mCA of smaller dimension as well as somatic mutations.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None declared.

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Author Contributions

A.L., S.M., P.S.: conceptualization, data curation, analysis, writing original draft. Q.X., A.G., Z.S., methodology and manuscript editing; S.L.A., J.H.L., K.C., A.Y., M.W., K.S., T.T.P.: manuscript editing; K.C., T.T.P. funding acquisition.

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