Mechanisms of Ageing and Development 175 (2018) 24–34

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Review and meta-analysis of genetic polymorphisms associated with exceptional human longevity

Mary Revelas[a], Anbupalam Thalamuthu[a], Christopher Oldmeadow[b], Tiffany-Jane Evans[b], Nicola J. Armstrong[a,c], John B. Kwok[d,e], Henry Brodaty[a,f], Peter R. Schofield[d,e], Rodney J. Scott[g,h], Perminder S. Sachdev[a,i], John R. Attia[b,h], Karen A. Mather[a,*]

[a] Centre for Healthy Brain Ageing, School of Psychiatry, UNSW Medicine, University of New South Wales, Sydney, Australia
[b] Hunter Medical Research Institute, Newcastle, Australia
[c] Mathematics and Statistics, Murdoch University, Perth, Australia
[d] Neuroscience Research Australia, Randwick, Australia
[e] School of Medical Sciences, University of New South Wales, Sydney, Australia
[f] Dementia Centre for Research Collaboration, University of New South Wales, Sydney, Australia
[g] Faculty of Health, University of Newcastle, Newcastle NSW, Australia
[h] Hunter Area Pathology Service, John Hunter Hospital, Newcastle, New South Wales, Australia
[i] Neuropsychiatric Institute, Prince of Wales Hospital, Barker Street, Randwick, NSW, Australia

ARTICLE INFO

Keywords:
Centenarians
Longevity
Meta-analysis
ACE
APOE
FOXO3A

ABSTRACT

Background: Many factors contribute to exceptional longevity, with genetics playing a significant role. However, to date, genetic studies examining exceptional longevity have been inconclusive. This comprehensive review seeks to determine the genetic variants associated with exceptional longevity by undertaking meta-analyses.
Methods: Meta-analyses of genetic polymorphisms previously associated with exceptional longevity (85+) were undertaken. For each variant, meta-analyses were performed if there were data from at least three independent studies available, including two unpublished additional cohorts.
Results: Five polymorphisms, *ACE* rs4340, *APOE* ε2/3/4, *FOXO3A* rs2802292, *KLOTHO* KL-VS and *IL6* rs1800795 were significantly associated with exceptional longevity, with the pooled effect sizes (odds ratios) ranging from 0.42 (*APOE* ε4) to 1.45 (*FOXO3A* males).
Conclusion: In general, the observed modest effect sizes of the significant variants suggest many genes of small influence play a role in exceptional longevity, which is consistent with results for other polygenic traits. Our results also suggest that genes related to cardiovascular health may be implicated in exceptional longevity. Future studies should examine the roles of gender and ethnicity and carefully consider study design, including the selection of appropriate controls.

1. Introduction

Life expectancy in most societies has increased steadily in the last century due to improvements in medical care, nutrition and other factors, with many individuals living to an advanced old age in developed countries (e.g. Oeppen and Vaupel, 2002). However, during ageing there is a loss of homeostasis, which leads to diminished capacity to respond to stressors and increased vulnerability to age-related decline, disease and multimorbidity (Fabbri et al., 2015). Thus, there is concern about an ageing population posing an increasing medical and economic burden on society. However, many exceptionally long-lived individuals have delayed morbidity or have escaped age-related diseases (Andersen et al., 2012). They represent a unique human paradigm for identifying the determinants of longevity and healthy ageing. Studying these rare individuals may reveal novel pathways that lead to exceptional ageing, which ultimately may suggest strategies to mitigate or prevent age-related decline and disease and to promote healthy ageing.

1.1. The heritability of longevity

Family and twin studies suggest that genetics plays a role in life expectancy with heritability estimated at ~20–30% (Murabito and Lunetta, 2012). Interestingly, the genetic contribution is modest early

* Corresponding author at: Centre for Healthy Brain Ageing, School of Psychiatry, University of New South Wales, Sydney NSW 2052 Australia.
E-mail address: Karen.mather@unsw.edu.au (K.A. Mather).

https://doi.org/10.1016/j.mad.2018.06.002
Received 26 March 2018; Received in revised form 1 June 2018; Accepted 7 June 2018
Available online 08 June 2018
0047-6374/

in life but increases at a greater age (> 60) (Hjelmborg et al., 2006). Two studies of very long-lived individuals, the New England Centenarian Study and the Okinawa Centenarian Study have shown that siblings of centenarians have an increased probability of reaching 100 years of age when compared to individuals without such family histories of longevity (Perls et al., 2002; Willcox et al., 2006). Interestingly, there are gender differences in the roles genes play, with the heritability of becoming a centenarian higher for men (~0.48) than women (~0.33) (Sebastiani and Perls, 2012). Murabito and Lunetta, (2012) also found that heritability appears to increase with each 10-year increment in survival age for men but not women, suggesting that genetic effects on aging may be more substantial for men than women.

1.2. Genes associated with exceptional longevity

Genetic studies to date have focussed on linkage analysis, candidate gene approaches or genome-wide association studies (GWAS) to identify exceptional longevity genes. In general, these have produced inconsistent results apart from the apolipoprotein E (*APOE*) (e.g.Beekman et al., 2013) and the forkhead box O3 (*FOXO3A*) genes (e.g.Willcox et al., 2008). The aim of this review is to summarize our present understanding of the genetic factors affecting human exceptional longevity by undertaking a comprehensive meta-analysis reviewing all the major polymorphisms that were investigated in three or more independent human studies of individuals aged 85+ and above, who have exceeded the average life expectancy for individuals born in the early 20th century (Newman and Murabito, 2013).

2. Methods

2.1. Literature search

A comprehensive search of electronic databases (MEDLINE, NCBI and EMBASE) was conducted to identify all publications on genes associated with exceptional human longevity up to December 30th, 2017. The search strategy was based on combinations of the following keywords “longevity”, “centenarian”, “ageing”, “aging”, “gene”, “genetic”, “polymorphism” and “SNP”. The search was extended to include the bibliographies of all eligible studies. Reviews on longevity were also hand-searched to identify additional potentially relevant studies. Where necessary, authors were contacted directly for any additional data required. In addition, unpublished data from our own studies were included in this review (see below, Section 2.4).

2.2. Study selection: inclusion and exclusion criteria

The following inclusion criteria were used to select articles for the meta-analysis: (i) information was provided on the association between one or more genetic polymorphism(s) and human “longevity”; (ii) used a case-control design whereby centenarians or aged participants (85+ years) were the cases versus younger adult controls; and (iii) provided sufficient genotype data for calculating the odds ratio (OR) and 95% confidence interval (CI). Studies were excluded if (i) the distribution of genotypes in the control group were not in Hardy-Weinberg equilibrium (HWE); (ii) they lacked a control group; (iii) they had overlapping study populations; (iv) they had fewer than 100 cases; (v) the article was unavailable in English; or (vi) results were only described in conference abstracts.

2.3. Data extraction

The recommendations for Meta-analyses of Observational Studies in Epidemiology (MOOSE) were followed. All relevant studies were obtained and independently inspected by two authors (MR and KM) to determine whether they met the inclusion criteria. When available, the appropriate data were also extracted from published GWAS. Careful attention was taken to avoid overlapping studies. The following information was extracted: author, publication year, ethnicity of the population studied, sample sizes (cases and controls), baseline characteristics of the study population (e.g. gender) and the genotype/allele frequencies. Information on HWE was also extracted or calculated manually if not explicitly reported. Finally, any discrepancies were adjudicated with another author (AT) until a consensus was reached.

2.4. Additional unpublished data used in meta-analysis

Australian unpublished data were also used in the meta-analyses. Specifically, two studies were utilized that both recruited individuals using the compulsory electoral roll and Medicare lists in order to obtain a representative sample. Cases were obtained from the Sydney Centenarian Study (SCS) (Sachdev et al., 2013) and controls from the Hunter Community Study (HCS) (McEvoy et al., 2010); both of these studies recruited participants from the state of New South Wales, Australia. The SCS is comprised of individuals aged 95 years and over who were recruited into a study of successful ageing in Sydney. More details of the study are found in Sachdev et al. (2013). A subsample with available genetic data provided 256 long-lived cases with a European background (age range 95–106, mean age 97.5 years, 31% men). The HCS is a cohort of 3253 individuals (age range 55–85, mean age 66.3 years, 46% male) recruited from Newcastle. For more details of the HCS see McEvoy et al. (2010). For the purpose of this study a subsample of 1002 individuals aged 55–64 (mean age 59.8 years, 47% male) was used as controls.

Both of these cohorts have genome-wide genotyping data available. HCS samples were genotyped using the Affymetrix Axiom Kaiser array (California, USA) whereas SCS cases were genotyped using the Illumina OmniExpress array (California, USA), according to the manufacturer’s instructions. Both studies excluded genotyped SNPs if the call rate was < 95%, p-value for HWE was $< 10^{-6}$ and minor allele frequency was < 0.01%. Relatedness checks were undertaken and only one family member was retained for the analysis if first or second-degree relatives were identified. Ethnic outliers were detected and omitted via EIGENSTRAT analysis (Price et al., 2006). After QC checks, for SCS there was genotyping data on 640,355 SNPs whilst for HCS there was data on 739,276 SNPs. For both cohorts, imputation was completed using the HapMap2 reference data (release 22, build 36) using the same method as described in Mather et al. (2016). *APOE* genotyping in both the SCS and HCS was undertaken using the methods described in Sachdev et al. (2010) and Oldmeadow et al. (2014) respectively. The results of the analyses using these data are designated as ‘Present Study, 2017’.

2.5. Statistical analysis

Meta-analyses were conducted for polymorphisms investigated in at least three studies. The strengths of the associations between each gene polymorphism and longevity were estimated by allelic odds ratios and 95% CIs. Wherever possible, analyses were also stratified by ethnicity and gender. A fixed-effects model using the inverse variance method was used and the significance of the pooled OR was determined by the Z-test. The I^2 statistic was used to estimate the percentage of variation across the results due to study heterogeneity, rather than sampling error, with the degree of heterogeneity being defined as low (25%), medium (50%) or high (75%). No significant heterogeneity was defined as an I^2 value of less than 50% and/or a p-value < .05. Forest plots were prepared for each study. Evaluation of the winner’s curse phenomenon, which refers to the occurrence when the effect size for a newly described genetic association is overestimated by the earliest study compared to later studies, was examined by re-running the meta-analysis omitting the earliest study. Sensitivity analyses were performed after the sequential removal of each included study to assess the influence of each individual study on the pooled OR. Potential publication bias was evaluated by visual inspection of funnel plots and