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Research on ageing and longevity in Estonia

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Summary

Due to demographic changes, the population ageing process in Estonia accelerated rapidly at the end of the 20th century. In Estonia, research in gerontology and geriatrics has no long-standing tradition. In the beginning, social aspects like the pension system, coping strategies and well-being of aged people, were the research focus. More recently, epidemiological studies of diseases seen in the older population have been extensively conducted. In clinical medicine, the main research topics have been osteoporosis, Parkinson's disease, dementia and stroke.

In this review, changes in neuromuscular function and hormonal regulation during ageing, and the genetic aspects of the Estonian Longevity Study will be described. The aim of the current paper is to introduce the main fields of gerontological research in Estonia to allow better integration with other research groups.

Keywords: Estonia, Estonian longevity study, genetics of longevity, neuromuscular ageing.

Introduction

Estonia is experiencing one of the fastest population ageing processes in Europe. Due to demographic changes (intensive immigration of young people after World War II, negative net migration since the 1990s and a negative natural increase), population ageing in Estonia was delayed for 40 years, but accelerated rapidly at the end of the 20th century. People 65 years and older accounted for 17.2% of the total population in 2008. The mean life expectancy at birth was 74.1 years (68.6 for males, 79.2 for females) and at the age of 65 was 16.6 years (13.6 for males, 18.6 for females).[1] According to recent population trends, the proportion of people 60 years of age and older will reach 33% by 2050.

The demographic situation presumes that studies in gerontology and geriatrics should be prioritized in Estonia; however, this is a new scientific field.

Studies of population ageing were launched in the 1980s by Professor Kalev Katus. Social gerontological research was initiated at the end of the 20th century, including studies of pension system reforms[2,3] and coping strategies and well-being of the older population.[4–7] Some groups have studied the epidemiology of diseases among the older population,[8–10] whilst others have studied osteoporosis, osteoarthrosis and joint replacement,[11,12] stroke,[13] Parkinson's disease and dementia.[14–16] In biogerontology there are two main focuses – age-related changes in neuromuscular function (changes in muscles, bones and joints) and hormonal regulation, and genetic aspects of the Estonian longevity study.

Age-related changes in neuromuscular function and hormonal regulation

Ageing of skeletal muscle results in a progressive loss of mobility that decreases quality of life and has major economic and social consequences for the society at large. Human skeletal muscles undergo both structural and functional changes with ageing. Reduced strength and speed of contraction are two major functional impairments of elderly muscles.[17]

Age-related changes in twitch contractile properties and voluntary force-generation capacity of skeletal muscles have been evaluated. It has been demonstrated that in women a marked age-related reduction in maximal voluntary force-generating capacity of the plantar flexor muscles and speed of contraction of the electrically evoked twitch takes place after 40 years of age, while reduction in maximal force-generating capacity and speed of relaxation of the twitch occurs after 50 years of age.[18] Middle age is characterized by reduced capacity for electrically evoked twitch force-generation and potentiation and slowed speed of contraction of the plantar flexor muscles.[19] Gymnastic type physical activity does not have a

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marked effect on twitch contractile properties in young and middle-aged women.[20]

It has been suggested that the ability to develop rapid isometric force of the knee extensor muscles does not differ significantly in middle-aged and elderly women. In comparison with young women, middle-aged and elderly women have a reduced ability to use the potentiating effect of stretch-shortening cycle to vertical jumping performance during a counter-movement jump.[21] A significantly longer chair-rise time and lower maximal rate of vertical ground reaction force development while rising from a chair has been found in elderly patients with mild-to-moderate Parkinson's disease compared with healthy controls.[22] It has been suggested that co-ordination of hand and arm movements in elderly patients with mild-to-moderate Parkinson's disease could be improved when exercising on a special co-ordination therapy device.[23] Schalow *et al*.[24] demonstrated that special movement therapy can reduce tremor in elderly patients with Parkinson's disease.

During recent years, Estonian researchers have evaluated the possible relationship between body composition, bone mineral content (BMC) and bone mineral density (BMD) values, and adipocytokine and ghrelin concentration in middle-aged and elderly women. It has been suggested that circulating adiponectin concentrations increase with age in normal-weight middle-aged and older women. Adiponectin is independently related to age, leptin, and insulin resistance values in women across the age span and with different menstrual status.[25]

The circulating ghrelin concentration could be regarded as an indicator of decreased fat-free mass in healthy elderly females.[26] It has been demonstrated that initial adiponectin concentration, together with specific body composition characteristics, predict loss in BMC and lumbar spine BMD values, while initial leptin concentration, together with specific body composition parameters, determined the loss in total and femoral neck BMD values in physically active older women.[27]

Genetic aspects of longevity and the Estonian Longevity Study

In Estonia, with a population of slightly over 1.3 million, currently 1 in every 26 individuals is 80 years of age or older. It is likely that by the year 2040 the prevalence will double.[28] The ability to survive until old age appears to be the result of a complex combination of genetics, environment and lifestyle factors. Understanding the genetic architecture of the very old and identifying the molecular mechanisms of longevity is a potentially powerful approach for discovering and targeting the pathways mediating ageing and disease susceptibility and developing preventive and therapeutic agents that will allow more of the population to age in good health.

So far, most genetic studies of human longevity show contradictory results and very few loci have emerged from candidate gene studies to reveal any associations. The Estonian Longevity Study may provide some input into this.

Different model organisms (e.g. *C. elegans* and *D. melanogaster*) have been used for longevity studies, several genes with substantial beneficial effects have been proposed to exist and several candidate-genes have been put forward.[29–31] In *C. elegans,* manipulation of more than 100 genes has been found to be responsible for lifespan changes.[32] Invertebrate studies provide a rationale for a search to identify loci affecting longevity in humans.

Given the evidence for the genetic basis for longevity, we would expect the prevalence of favourable/protective genotypes (haplotypes) in genes contributing to prolonged lifespan (i.e. longevity haplotypes) to be significantly higher in an old cohort, relative to their prevalence in younger population-based control subjects. In contrast, deleterious genotypes associated with the 'ageing phenotype' (age-related disease genes) would be expected to decrease as mortality selects out individuals with these deleterious genotypes. The protective genotypes/haplotypes together with lifestyle/environment factors may avoid the early onset of diseases and death at a younger age. This hypothesis could lead to the discovery of not only the relevant genotypes/haplotypes/genes but also the environment (and/or lifestyle)–gene and gene–gene interactions. These considerations suggest that changes in genotypic frequencies affecting lifespan in different age groups can be detected and used to determine the relevant genomic markers associated with the longevity process. In addition, it has been shown that changes on an epigenetic level may play a role in achieving longevity as these modifications are essential for normal growth and development[33] and alterations are associated with various pathologies, including cancer.[34]

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Achieving longevity is a very complicated process involving molecular mechanisms of the whole organism. Thus it is important to analyse the maximum number of genomic markers using whole-genome genotyping or deep resequencing in order to discover genetic variations and gene–gene interactions. Structural changes in genomic level may identify and explain the molecular processes occurring during ageing and achieving longevity.

In the first phase of the Estonian Longevity Study, 500 females over the age of 80 will be analysed using high density genotyping microarrays (www.illumina.com) and control subjects are from an already genotyped population-based group.

Estonian biobank as a valuable resource for genetic studies

The Estonian Genome Project has a biobank (www.geenivaramu.ee), which consists of 41,000 gene donors. It is one of the biggest population-based biobanks in Europe, as it already includes 4% of the adult population. The Estonian biobank has well phenotyped gene donors (over 300 phenotypes) with broad informed consent, which enables researchers to carry out comprehensive studies of complex phenotypes (like longevity). Currently, the biobank consists of 1069 individuals (729 females and 340 males) aged 80 years or older. This older group is growing, as more individuals become gene donors.

Selection of the cases and controls

Genetic influences on lifespan become apparent only after the age of 60 years.[35] As the life expectancy in Estonia is 79.2 for females and 68.6 for males,[1] it is reasonable to study individuals over the age of 80 years, as these represent a very specific population. At the same time, environment and lifestyle also play important roles in lifespan. However, this is still related to genetics, since susceptibility to environmental factors is also determined by genes and gene–gene interactions.[36,37] Environmental factors associated with extreme survival in humans are avoidance of heavy smoking and severe obesity.[38] Studies with model organisms have suggested that caloric restriction extends lifespan by increasing resistance to reactive oxygen species (ROS) and/or by reducing the production of ROS.[39,40]

In the biobank, all elderly participants undergo a computer-assisted genetic epidemiological questionnaire. The control group is selected from participants under the age of 45 years, in whom family history (e.g. parental and grandparental age or their age at death), lifestyle and environmental factors are well documented.

Population stratification

Population stratification has been a subject of discussion for many years as the potential confounding factor for association studies.[41,42] Several papers have been published recently to demonstrate the extent of the genetic stratification in European populations and among Estonians.[43–45] These demonstrated that populations geographically close to each other have no substantial stratification. A study by Nelis *et al.*[44] found that Estonians are genetically very homogenous (λ is 1.04) and only marginally different from Latvians (λ is 1.2), compared, for example, to Spaniards (λ is 2.5).

Gender differences

Gender-specific differences do exist at the genomic level between males and females and have to be taken into account in genetic association studies. It is well known that gender-specific genetic architecture influences the outcome (prevalence, age of onset and severity) of reproductive, physiological and disease traits. For example, cardiovascular disease is predominant in men throughout adulthood, but has a higher rate of occurrence in post-menopausal women;[46] in adulthood, major depression and Alzheimer's disease are more common in women,[47,48] whereas schizophrenia and Parkinson's disease are more prevalent in men.[49,50] Therefore, we decided to study women to keep the study group homogenous and avoid gender-specific confounding effects.

Selection of the analysis method

Based on *A Catalogue of Published Genome-Wide Association Studies*,[51] only two genome-wide association studies (GWAS) have been conducted on longevity-related traits. So far, candidate gene studies have been more prevalent, but still lack good associations. The most consistent evidence for association with longevity has been found only for the *APOE*[52,53] and *FOXO3A*[54–57] loci.

The GWAS have been used to study complex traits such as longevity since 2005. Analysing different genomic structural variations, such as

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single nucleotide polymorphisms (SNP), copy number variations (CNV), loss of heterozygosity (LOH) and runs of homozygosity (ROH), may illustrate significantly associated loci with longer lifespan. The Institute of Molecular and Cell Biology is part of the Centre of Excellence in Genomics, which makes available the whole-genome genotyping (high density microarrays with more than 660,000 genomic markers) and resequencing platforms using Illumina technology to reveal the associated genomic structural variations. Resequencing can then be used to find the causative and/or functional loci. Such loci may point to pathophysiological processes or pathways that contribute to increased risk of, or protection from, morbidity and mortality in human populations. Such processes may eventually be modifiable in early stages of the ageing process to promote healthy ageing.

Conflicts of interest

All authors declare no conflicts of interest.

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