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Healthy ageing, the genome and the environment

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Abstract

The sequenced genomes of individuals aged 80 years, who were highly educated, self referred volunteers and with no self reported chronic diseases were compared to young controls. In these data, healthy ageing is a distinct phenotype from exceptional longevity and genetic factors that protect against disease might be enriched in this population.

Exceptional longevity is an easily measured phenotype in countries that have reliable population-based data registries. These data have enabled the pooling of genome-wide association studies (GWAS), but even when the combined sample size is large, very few common genetic variants associated with longevity have been identified, and all have modest effect sizes¹. Of greater interest and benefit to individuals and society than simply how long one lives is whether one is ageing healthily. The study by Erikson and colleagues involving an unprecedentedly large whole-genome sequencing (WGS) comparison of 511 individuals who are ageing healthily and nearly 700 controls is, therefore, a welcome and novel addition to the literature on the genetics of ageing².

In the study, the authors define a ‘welderly’ individual as being 80 years old who did not have any of a series of chronic diseases or was receiving medications. Being free of disease and older than 80 years of age seems to be a safe definition of healthy ageing. Nevertheless, whether an octogenarian individual is judged to be free of disease could hinge very much on diagnostic intensity, and the welderly designation in this study was self-reported. In a population-based study of >700 individuals aged 85 years from Newcastle, UK³ no participant after clinical examination was found to be free of all 18 diseases considered (including cancer, ischaemic heart disease, hypertension, diabetes mellitus, dementia, osteoporosis and arthritis) even though 40% of individuals rated their health as ‘excellent’ or ‘very good’ compared with others in their age group. Furthermore, the investigators found

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Competing interests statement

The authors declare no competing interests.

that many diseases might be severely underdiagnosed in this population. For example, atrial fibrillation was evident on electrocardiography in 14% of participants, of whom 28% had no such diagnosis in their general practice records. Arguments exist, therefore, for expanding the definition of healthy ageing beyond simple disease status. Physical and cognitive functioning are much more strongly associated with survival in the oldest individuals than presence or absence of disease⁴, and these functions make essential contributions to quality of life.

To show that healthy ageing was not merely the result of pure luck, Erikson *et al.* had the welllderly report on their siblings' mortality. Compared with the 1920s birth cohorts in the USA, the siblings of the welllderly had lower mortality. For instance, 83% of the welllderly siblings survived from age 10 to 70 years compared with 75% in the 1920s cohorts, indicating familial aggregation. Genetic variants influencing longevity might be reasonable candidates for healthy ageing. However, the investigators did not find any associations between the healthy ageing phenotype and the few longevity-associated gene variants that are currently known, such as *FOXO3A* — except for the most strongly-associated longevity variant, *APOE*. This result led the team to conclude that healthy ageing is an overlapping, but distinct phenotype, from exceptional longevity. That healthy ageing is distinct from simply living for a long time is without dispute: after all, any individual could be struck by lightning or be involved in a fatal accident on their way to the tennis court. Nonetheless, healthy ageing and exceptional longevity are also very much related. People who live to

100 years of age, for example, generally represent individuals who age healthily. A nationwide, registry-based study of an unselected sample of more than 40,000 individuals born in 1905 and followed up from 1977 through to 2004 showed that those surviving to become centenarians, when in their 70s, had hospitalization rates that were lower in a dose-response manner than individuals from the same birth cohort who died in their 80s or 90s. For example, only 6% of those who survived to become centenarians were hospitalized >5 days at age 71–74 years, whereas this number was 17% for those dying at age 80–84 years and 9% for those dying at age 90–94 years⁵.

Erikson and colleagues could not identify associations with most known longevity variants, which might reflect the distinct nature of longevity and healthy ageing. Alternatively, the result could be a consequence of the sample size, which although large for a WGS ageing study, would be considered quite small for the purpose of detecting genetic variants. Interestingly, although no single locus was found to be of genome-wide significance when comparing welllderly individuals to controls, variants associated with cognitive function were significantly over-represented among their top GWAS hits such as a linkage block at MHC locus 6p22.1. The maintenance of cognitive function might be a key contributor to healthy ageing. Nevertheless, the method by which the sample was identified might also have contributed to the results on cognition. The individuals defined as welllderly in this study were recruited through various media solicitations (such as radio, newsletter, newspaper advertisements). A non-random sub-sample of the population is known to respond to such solicitations⁶ and that seems to be the case here. Among the welllderly in the study by Erikson *et al.*, 82% had a college degree versus just 19% in the background population². On this background, that the welllderly were enriched with genetic factors associated with cognitive function might not be surprising, especially given that in the

control group of 20–44 year olds, one-third were parents of a preterm neonate, a group of individuals who are known to be associated with an adverse socioeconomic position⁷. As the welllderly population increases in size and the statistical power to detect genetic variants increases, confirming that the cognitive function results are meaningful in healthy ageing, rather than simply the peculiarities of sampling, will be important.

Welllderly individuals might be distinguished as much by the lifestyles they lead as the genes they inherit. For example, in a 2015 population-based study that included the offspring of long-lived siblings (surviving to at least 90 years of age) the offspring had one third of the expected lung cancer incidence⁸. As the incidence of lung cancer is strongly correlated with lifestyle, these findings suggest that a healthy lifestyle might be a main driver for the familial clustering of exceptional good health. A similar phenomenon might be operating in the welllderly sample, which was distinguished by a high prevalence of exercise (67% versus 44% in controls) but, surprisingly, also by slightly increased rates of having ever smoked tobacco in men (61% versus 54% in controls) and no difference among women (42% versus 43%). However, high educational attainment is also associated with quitting smoking, so a high proportion of the highly educated welllderly might be ex-smokers. It therefore seems likely that the very highly educated welllderly individuals are healthier than their age peers in terms of current or lifetime exposure to tobacco smoking, but these data are unfortunately not reported in the Erikson *et al.* study. Nevertheless, as this study progresses, these data will provide a valuable opportunity to explore how lifestyle factors combine and interact with genetic factors to establish a healthy ageing phenotype.

With the lengthening of the human lifespan, comes a need to understand not only how we can live long, but also how we can live well. The comprehensive WGS study by Erikson and colleagues provides an important first step to create a shared data resource for identifying the common and rare genetic variants associated with healthy ageing. Progress will be most rapid when findings from WGS studies are combined with those from other genetic approaches, such as ongoing studies in longevity-enriched families, which have already been successful in identifying rare or novel genetic variants of importance to healthy ageing⁹. Ultimately, an understanding of both genetic and lifestyle factors will be needed to unravel the underlying mechanisms of long and healthy lives.

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References

1. Deelen J, et al. Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. *Hum Mol Genet.* 2014; 23:4420–4432. [PubMed: 24688116]
2. Erikson GA, et al. Whole-genome sequencing of a healthy aging cohort. *Cell.* 2016; 4:1002–1011.
3. Collerton J, et al. Health and disease in 85 year olds: baseline findings from the Newcastle 85+ cohort study. *BMJ.* 2009; 339:b4904. [PubMed: 20028777]

4. Thinggaard M, et al. Survival prognosis in very old adults. *J Am Geriatr Soc.* 2016; 64:81–88. [PubMed: 26782855]
5. Engberg H, Oksuzyan A, Jeune B, Vaupel JW, Christensen K. Centenarians — a useful model for healthy aging? A 29-year follow-up of hospitalizations among 40,000 Danes born in 1905. *Aging Cell.* 2009; 8:270–276. [PubMed: 19627266]
6. Ganguli M, Lytle ME, Reynolds MD, Dodge HH. Random versus volunteer selection for a community-based study. *J Gerontol A Biol Sci Med Sci.* 1998; 53:M39–M46. [PubMed: 9467432]
7. Joseph KS, et al. Effects of socioeconomic position and clinical risk factors on spontaneous and iatrogenic preterm birth. *BMC Pregnancy Childbirth.* 2014; 14:117. [PubMed: 24670050]
8. Pedersen JK, et al. Low tobacco-related cancer incidence in offspring of long-lived siblings: a comparison with Danish national cancer registry data. *Ann Epidemiol.* 2015; 25:569–574.e3. [PubMed: 25890797]
9. Druley TE, et al. Candidate gene resequencing to identify rare, pedigree-specific variants influencing healthy aging phenotypes in the long life family study. *BMC Geriatr.* 2016; 16:80. [PubMed: 27060904]