Longevity Families of the Netherlands

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To identify causal socio-genetics longevity mechanisms protecting from (multi)morbidity in humans:1. The primary objective is to disentangle novel rare-, and structural gene variants that can explain longevity and protection from (multi)morbidity in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON53902

Source
ToetsingOnline

Brief title
LOF-NL

Condition

- Other condition
- Economic and housing issues

Synonym
ageing, healthy ageing

Health condition

veroudering, leeftijdsgerelateerde ziektes

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: ageing, biomarkers, gene discovery, healthy ageing

Outcome measures

Primary outcome

Our primary analyses are A) within cases: a non-parametric linkage analysis to establish likely genomic regions of longevity genes in researched families, to this end we will solely use the families defined as cases (LRC>=30%). B) between cases and control: we compare social and behavioural factor that associate with familial longevity in the cases and controles. A Genetic analysis. Primary analysis. In the linkage analysis you compare familymember on marker positions , bases on single-nucleotide polymorphism (SNP) -arrya genotyping data, and you test whether the 'longevity-affected- familymember share more alleles than chance (allele frequentie in the population) then expected on these marker positions. The more member from one family you can include the more power you will have in you analysis. From this comes a logarithm-of-the-odds (LOD)-score. We shall focus on regions with a peak LOD-score of 3 or higher (this indicates that it is at least 1000x likely that the longevity gene lies on that position and not somewhere else on the genome) and encompasses a region between the peak and 1-LOD-drop. In the DNA of member of these families contributing to these linkage signals we shall perform whole-genome-sequencing (WGS). From this sequencing data we shall select genetic variant that are shared between all familymember that positively contribute to the linkage signals. Relevant genevariants shall be selected within the linkage-regions in one of two ways. Firstly, we shall select very rare genvariant that have a predicted functional

through an in sillico procedure, based on predicted rare protein altering gene variants (minor allele frequency (MAF) < 0,2%)> Secondly we select on more common variants (common SNPs) in chromosome regions under the linkage signals. Secundaire analyses: Variants in the same gene in multiple families contributing to the linkage signals shall be candidates for further studies into the function of how these genes contribute to healthy ageing. We shall compare carriers of relevant variants versus non-carriers within the LOF-NL study or in existing data of, among other, the Leiden Longevity Study (LLS), to research whether whether these variants associatie with changes in RNA expression of the genes or changes in health calculated from grip strength measurements and 'moleculaire clocks or predictors' that are predicitve for frailty, mortality and disease outcomes. In this we we can get an indication of health while the measurements are minimal invasive. The new moleculair predictors shall be mainly base on nuclear magnetic resonance (NMR)- based metabolomics score (MetaboHealth, MetaboAge) with in the future space for clocks based on DNA methylation, transcriptome and proteome based predictors. B) Analysis of socio- and behavioralfactors. Primaire analysis. We compare 75+ year old cases from long-lived families (LRC>=30%) with 75+ year old controls from average families (LRC=0%) on different socio- and behavioralfactors that are measured through questionnaires. Secundaire analyses: Firstly we will look into SNP array data from cases and control whether there is a difference in polygenic risk score (PRS) that explain the heritable component of personality and behaviour. A PRS is a summation of multiple genetic variants (SNPs) that are associated with a phenotype. A PRS reflects the genetic predisposition of a

certain trait, that can be used as a predictive factor for that trait, which in this case are social and behavioral traits that can contribute to a high LRC-score and can contribute to longevity. A second secondairy analysis concers the health of cases and controls. To get a indiclation of differences in health without the need of withdrawing blood we shall do an associationanalysis based on DNA-methylation profiles in DNA collected from saliva that can be collected in the cases and controls. The on DNA-methylome based health status in cases and controls can be coupled on differences in social- behaviour and status within these groups.

Secondary outcome

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Study description

Background summary

The demographic life expectancy enhancement of the past 150 years imposes an urgent challenge in Western and economically growing societies to stimulate the healthy lifespan that is lagging behind. Families surviving into exceptionally high ages (longevity) in good physical and mental health illustrate that this is physiologically possible. Such families harbor cross generational socio-genetic mechanisms that mediate healthy aging and protection from (multi)morbidity. Identifying the genetic loci contributing to extended health- and lifespan in the population at large is challenging due to the uncertainty in defining long-lived cases with the heritable longevity trait amongst long-living phenocopies. So far, only variants in the APOE and FOXO3 were consistently identified. These loci do not explain the full quantitative longevity trait that we observed being transmitted in families. In the past we have built up a study of longevity families (the Leiden Longevity Study). We will expand the collection of such families using a more strict definition of heritable longevity to be used in genetic studies.
As a first step to improve the potential for finding novel longevity loci in socio-genetic research, for the past 5 years we explored the nature of familial transmission of longevity in historical genealogical data and we generated a

novel longevity case definition. For practical applications we developed the Longevity Relatives Count (LRC) -score which is based on the number of long-lived ancestors of a proband case. An LRC of 30% indicates that 30% of ancestors of a proband survived into the top 10 % survivors of their birth cohort. By applying our LRC-score in the genealogical data, we identified families and elderly persons that meet the novel criteria of heritable longevity and likely harbour longevity loci protecting against (mutli)morbidity.
Here we propose that in order to identify the causal factors driving familial longevity, we collect an LRC based selection of highly aged cases and their families for the purpose of performing genome wide genetic studies to identify longevity loci along with a focus on socio-economic behaviour and environmental background of longevity families, which has not as yet received sufficient attention so far,

Study objective

To identify causal socio-genetics longevity mechanisms protecting from (multi)morbidity in humans:
1. The primary objective is to disentangle novel rare-, and structural gene variants that can explain longevity and protection from (multi)morbidity in the families.
2. The secondary objective is to focus more in depth on socio-behavioural and environmental components of familial longevity, their role in (multi)morbidity and interaction with the genetic longevity component.
3. The third objective is to extend objective 1 also to common variants and to link the socio-behavioural and genetic longevity components to metabolomics and epigenetic health biomarkers.

Study design

Family based observational study consisting of cases from families with multiple long-lived ancestors (LRC>=30%) and controls from families with no long-lived ancestors (LRC=0%).

Study burden and risks

There are no direct benefits to the subjects. We include a limited number of questionnaires about socio-economic status and lifestyle, which might be experienced as burdensome for some participants. Blood withdrawal of 3 tubes with in total 22,5 mL will be performed, which is a minimally invasive procedure. Social network questions might be confronting for some of the participants.

Contacts

Public
Leids Universitair Medisch Centrum

Einthovenweg 20
Leiden 2333ZC
NL
Scientific
Leids Universitair Medisch Centrum

Einthovenweg 20
Leiden 2333ZC
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

Longevity Relatives Count (LRC) expresses a score indicating the percentage of ancestors surviving into a specific top percentile of their birth cohort. We focus on LRC 30%.

Cases LRC>=30%:
- Able to give written consent
- Willing and able to follow the study protocol
- LRC-score 30% and up in
- Age >= 75 years
- At least one sibling or first cousin with age >= 75 years who has given written consent

Controls LRC=0%:

- Able to give written consent
- Willing and able to follow the study protocol
- LRC-score 0% in our
- Age >= 75 years

Exclusion criteria

- Not be able to give (written) informed consent

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-12-2023
Enrollment:	770
Type:	Actual

Ethics review

Approved WMO

Date:	16-08-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO Date:	08-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	27-01-2025
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL81887.058.23