Genetic determinants of healthy longevity

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SAMENVATTING

INTRODUCTIE

Naast toeval, gedrag en omgeving bepalen erfelijke factoren de lengte en kwaliteit van het menselijk leven. In sommige families bereiken opvallend veel mensen een hoge leeftijd ('langlevendheid') en kinderen van lang levende ouders hebben zelf een grotere kans gezond oud te worden dan hun generatiegenoten. Kennis over de erfelijke factoren die langlevendheid beïnvloeden kan bijdragen aan het ontwikkelen van methoden voor het bereiken van een hoge leeftijd in goede gezondheid. Tot heden is onbekend welke genen bijdragen tot gezonde langlevendheid in de mens.

Het grootste gedeelte van het erfelijk materiaal is voor ieder individu hetzelfde en verklaart de grote gelijkenis tussen mensen in vergelijking met andere soorten. Maar tussen individuen is ongeveer 1 op de 300 basenparen verschillend, oftewel polymorf. Deze polymorfismen verklaren waarom individuen verschillend zijn en kunnen worden gebruikt om de functie van de verschillende genen te achterhalen en hun rol in het bepalen van uiterlijke kenmerken en ziekte, maar ook van levensduur en gezondheid. Ieder gen is in principe kandidaat om de lengte en kwaliteit van leven te beïnvloeden, maar het bestuderen van alle vijfentwinitig duizend humane genen is vooralsnog te tijdrovend en te duur. Identificatie van specifieke kandidaat genen is efficiënter.

In diermodellen wordt veel onderzoek gedaan naar de biologische mechanismen die levensduur bepalen. Deze biologische mechanismen zijn gedurende de evolutie geconserveerd gebleven en komen ook bij andere soorten, waaronder de mens, voor. Het **doel van dit proefschrift** is het identificeren van menselijke kandidaat-genen voor langlevendheid, door het vertalen van wetenschappelijke resultaten verkregen in diermodellen. Deze kandidaatgenen werden vervolgens bestudeerd in de Leiden 85-plus Studie. Aan deze studie namen bijna alle Leidenaren deel die tussen 1997 en 1999 de leeftijd van 85 bereikten. Van hen werd op 85-jarige leeftijd DNA en bloedmonsters afgenomen, en daarna werd jaarlijks vervolgd met betrekking tot hun dagelijks functioneren, cognitie, ziekte en sterfte.

Het onderzoek beschreven in dit proefschrift werd uitgevoerd in het kader van een Innovative Oriented Research Program (IOP), waarin biologen, genetici en artsen samen op zoek gingen naar erfelijke factoren die levensduur beïnvloeden. Het onderzoek werd geiniancierd door het Ministerie van Economische zaken en een aantal industriële

partners, met als doel samenwerking te bewerkstelligen tussen academie en industrie en het genereren van kennis die economisch te gelde kan worden gemaakt.

INHOUD

De rondworm *Cenorhabditis elegans* wordt veel bestudeerd in het onderzoek naar erfelijke determinanten van langlevendheid. De worm doorloopt een goed omschreven ontwikkeling en is uitermate toegankelijk voor wetenschappelijke experimenten zoals het stilleggen of modificeren van complete genen, iets dat bij de mens ethisch gezien onmogelijk is. Onder normale omstandigheden ontwikkelt de worm zich via vier larvale stadia in een volwassene. Onder ongunstige omstandigheden (voedsel tekort, ongunstige temperatuur) kan de worm een alternatieve larvale vorm aannemen, de dauer diapause, waarin de worm niet eet, nauwelijks beweegt, niet voortplant en zeer ongevoelig is voor schadelijke factoren uit de omgeving. In deze periode lijkt de worm niet te verouderen, want als de omstandigheden weer gunstig worden hervat de worm zijn normale ontwikkeling en wordt een volwassene met een normale levensduur bovenop de periode die in duaer diapause is doorgebracht. In *C. elegans* zijn veel mutaties in genen beschreven die de levensduur van de volwassen worm kunnen verlengen tot vijfmaal de normale levensduur, voornamelijk door het beïnvloeden van de dauer fase (derhalve “daf” genen genaamd).

DAF-12 is een gen in de rondworm dat functioneert op het kruispunt van vele signaal systemen en deze integreert tot een beslissing om al dan niet in dauer fase te gaan. Menselijke genen die lijken op DAF-12 zijn dus belangrijke kandidaten om ook in de mens levensduur te beïnvloeden. In **hoofdstuk 2** identificeren we menselijke genen die lijken op DAF-12. Het daf-12 gen codeert voor een Nucleaire Hormoon Receptor (NHR) en behoort tot een superfamilie van NHR’s is die bij alle soorten voorkomen, waaronder de mens. Door de volgorde van aminozuren te vergelijke waaruit deze NHR’s zijn opgebouwd, ontdekten we dat in de mens de Lever X Receptoren alfa en bèta het meest lijken op *C. elegans* DAF-12, gevolgd door de Pregnaan X Receptor, de Vitamine D Receptor, de Constitutieve Androstaan Receptor en de Farnesoid X Receptor. Hun biologische functie omvatten, onder andere, detoxificatie en immuno-modulatie. Dit zijn beide belangrijke processen bij het beschermen van het lichaam tegen schadelijke invloeden van buitenaf. Opvallenderwijs hebben alle humane NHR’s een cholesterolproduct als activator of suppressor. Derhalve concludeerden we dat het DAF-12 systeem gedurende de evolutie ook functioneel geconserveerd lijkt en dat de humane NHR’s betrokken zijn in kritieke processen voor het menselijk lichaam. Genetische variatie in deze NHR’s zijn dus belangrijke kandidaten om langlevendheid te beïnvloeden.

De Vitamine D Receptor (VDR) is een van de menselijk eiwitten die op DAF-12 lijken. Vitamine D is in de mens, onder andere, betrokken bij het functioneren van het brein. In **hoofdstuk 3** bestudeerden we of genetische variatie in de VDR geassocieerd is met cognitieve functie en depressieve symptomen op hoge leeftijd. Vijf polymorfismen, te weten *Cdx-2*, *FokI*, *BsmI*, *ApaI* and *TaqI*, waarvan de laatste drie samen een geconserveerde regio markeren (een haplotype blok), werden bepaald in alle deelnemers van de Leiden 85-plus Studie. Het bleek dat dragers van haplotype 2 een slechtere cognitieve functie hadden, terwijl haplotype 1 juist associeerde met een betere cognitieve functie en minder depressieve symptomen. Deze associaties konden niet worden verklaard door verschillen in calcium niveaus of sterfte, omdat de polymorfismen daarmee niet associeerden. Deze resultaten lieten zien dat genetische variatie in de VDR invloed heeft op de vatbaarheid voor leeftijdsafhankelijke veranderingen zoals cognitief functioneren en depressieve symptomen.

In **hoofdstuk 4** onderzochten we of genetische variatie in de Lever X Receptor alfa (LXRα) associeert met langlevendheid. De LXRα is het menselijke eiwit dat het meest lijkt op *C. elegans* DAF-12. In deelnemers van de Leiden 85-plus Studie bepaalden we vier polymorfismen, die samen vier gangbare haplotypes markeren. Het bleek dat haplotype 2 associeerde met een 22% verminderd mortaliteitsrisico in de zeven jaar na het begin van de studie. Dit werd voornamelijk veroorzaakt door een 69% verminderd risico op overlijden aan infectieziekten. Bovendien associeerde haplotype 2 ook met een hoger plasma niveau van apolipoproteine E, een eiwit waarvan de productie wordt gereguleerd door LXRα, en hogere niveaus van triglyceriden. Concluderend, genetische variatie in het gen dat codeert voor de LXRα associeert met langlevendheid.

Een van de genen waarvan de functie wordt beïnvloed door de LXRα is apolipoproteine E (apoE). Drie structurele varianten van apoE (apoE2, E3, and E4) worden gecodeerd door drie genetische varianten (resp. ε2, ε3 en ε4) en behoren tot de meest bestudeerde polymorfismen in de mens. ApoE4 associeert met een slechtere cognitieve functie en een verhoogde kans op cardiovasculaire mortaliteit. Opvallend is dat er, in tegenstelling tot over de structurele variatie, over de invloed van de kwantiteit van apoE weinig bekend is. In de **hoofdstukken 5, 6 en 7** bestuderen we de rol van plasma niveaus van apoE in respectievelijk cardiovasculaire mortaliteit, cognitief functioneren, en het optreden van herseninfarcten. Hiertoe bepaalden we in alle deelnemers van de Leiden 85-plus Studie op 85-jarige leeftijd het APOE genotype, het apoE plasma niveau en vervolgde vervolgens de genoemde eindpunten.

In **hoofdstuk 5** beschrijven we dat deelnemers met hoge plasma apoE niveaus een 2.08 maal zo hoog sterfterisico hebben dan deelnemers met lage apoE niveaus. Onder de deelnemers die het ε3ε3 genotype droegen, was het risico op cardiovasculaire sterfte 3.01 maal verhoogd. Andere sterfteoorzaken waren niet verhoogd. Hoge apoE niveaus waren geassocieerd met hoog totaal cholesterol, LDL cholesterol en triglyceriden en met lage HDL-cholesterol niveaus, maar deze associatie kon het verband tussen hoge apoE niveaus en cardiovasculaire sterfte niet verklaren. Het risico op cardiovasculaire sterfte was het sterkst in de deelnemers met een laag niveau van het C-reactive protein (CRP), een ontstekingsparameter en bekende risico-indicator van hart- en vaatziekten. Bovendien was in deelnemers met een laag CRP aan het begin van de studie, de toename in CRP tijdens de follow-up het hoogst in de deelnemers met hoge plasma apoE niveaus. Concluderend, op hoge leeftijd gaat een hoog apoE niveau vooraf aan een hoog CRP niveau en associeert sterk met een toegenomen risico op cardiovasculaire sterfte.

In **hoofdstuk 6** bestudeerden we van iedere deelnemer vanaf de leeftijd van 85 jaar en daarna ieder jaar de cognitieve functie. Dit gebeurde aan de hand van een gestandaardiseerde cognitieve testbatterij, waarvan de Mini Mental State Examination (MMSE) de bekendste is. Onder dragers van het ε3ε3 genotype associeerde een hoog plasma apoE niveau met een slechtere cognitieve op alle testen. Klassieke cardiovasculaire risicofactoren konden deze associaties niet verklaren. Een andere mogelijke verklaring werd gezocht in het risico op het krijgen van herseninfarcten. In **hoofdstuk 7** observeerden we dat deelnemers met een hoog apoE niveau bij aanvang van de studie een 1.47 maal hogere kans hadden op het hebben van een herseninfarct in de voorgeschiedenis. Gedurende de follow-up waren hoge plasma apoE niveaus geassocieerd met een hogere kans op het krijgen van een herseninfarct. Het verhoogde risico op herseninfarcten dat eveneens gepaard ging met hoge plasma niveaus van apoE kon de associatie met lagere cognitie niet verklaren.

Een ander gen dat onder invloed staat van LXRα is apolipoproteine CI (apoCI). ApoCI maakt onderdeel uit van voornamelijk HDL deeltjes, en in muizen beschermt het tegen sterfte door ernstige ontstekingen. In **hoofdstuk 8** onderzochten we of hoge plasma niveaus van apoCI ook in mensen beschermend werken tegen sterfte aan infectieziekten in de Leiden 85-plus Studie. Het bleek dat het hebben van hoge plasma apoCI niveaus associeerde met een 40% reductie in sterfte aan infectieziekten, onafhankelijk van andere lipidenparameters, zoals HDL-cholesterol. Concluderend, hoge waardes van apoCI lijken ook in de mens te beschermen tegen sterfte aan infectieziekten op hoge leeftijd.

In **hoofdstuk 9** beschouwen we de genen die evolutionair geconserveerd zijn en die betrokken zijn in de regulatie van langlevendheid in diermodellen en bestudeerd zijn in de mens. Biologische mechanismen die tot dusver zijn geïdentificeerd spelen een rol in stofwisseling en in onderhoud en reparatiemechanismen, die de leeftijdsgerelateerde ophoping van schade beperken. De literatuur beschouwend kan geconcludeerd worden dat met het complexer worden van de soorten in het verloop van de evolutie, ook het genetisch materiaal complexer is geworden. Waar bijvoorbeeld in de worm slechts een gen een bepaalde functie vervult, zijn dat er in de mens soms vier. Dit resulteert erin dat genetische variatie in een van die vier genen minder grote invloeden zal hebben op langlevendheid dan genetische variatie in het oorspronkelijke gen. Een andere factor die het vertalen van resultaten van dier naar mens bemoeilijkt is de omgeving. De functie van het genoom is kritisch afhankelijk van de omgeving waarin het zich bevindt. De omgeving waarin sommige van onze voorouders zijn geselecteerd is totaal anders dan onze huidige omgeving. En zelfs onze omgeving van nu is niet dezelfde als 100 jaar geleden. Dit zorgt ervoor dat resultaten verkregen in diermodellen onder laboratoriumomstandigheden niet altijd hetzelfde resultaat opleveren als de observationele studie in de mens. Tenslotte, de methoden die ons ter beschikking staan om genetische variatie te bestuderen in de mens zijn vooralsnog beperkt, duur en tijdrovend. Concluderend kan gezegd worden dat, hoewel het bestuderen van diermodellen een aantal mogelijke kandidaat genen heeft opgeleverd, het onduidelijk blijft in welke mate zij langlevendheid in de menselijke populatie bepalen.

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DANKWOORD

Onderzoek is niet mogelijk zonder mensen die zich laten onderzoeken. Mijn dank gaat dus in eerste instantie uit naar de deelnemers van de Leiden 85-plus Studie. Een deel van hen heb ik mogen ontmoeten en onderzoeken en deze ontmoetingen hebben voor mij kleur gegeven aan het onderzoek en mij warm gemaakt voor het vak Ouderengeneeskunde.

Vele mensen waren betrokken bij de opzet en uitvoering van de Leiden 85-plus Studie, ook voor mijn komst naar de afdeling. Hen ben ik zeer dankbaar.

Mijn collega's op de afdeling Ouderengeneeskunde en daarbuiten dank ik voor de plezierig werkomgeving en inspirerende samenwerking.

Het onderzoek in dit proefschrift werd uitgevoerd onder de vlag van het IOP project "genetic determinants of longevity and disease at old age". Hierin werkten biologen, genetici en dokters samen om het geheim van een gezonde oude dag te ontrafelen in fruitvlieg, vlinder en mens. Een interessante mix van mensen uit verschillende wetenschappelijke werelden met vele interessante discussies en samenwerkingen als gevolg. Iedereen die daaraan bijdroeg wil ik hartelijk danken.

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The author was born in Oegstgeest on January 13th 1974. In 1992 he graduated from the Stedelijk Gymnasium in Leiden. In these years he studied Medicine at the Rijks Universitair Centrum Antwerpen (RUCA), in Antwerpen Belgium and Biomedical Sciences at the Leiden University Medical Center (LUMC). In 1994 he started his Medical education at the LUMC, during which he was actively involved in the organization of the educational system. In 1997 he postponed his study for a year to be the "student-assessor" to the board of directors of the Leiden University Medical Center. In April 2002 he received his MD degree.

In the same year he got a position as a PhD at the Department of Gerontology and Geriatrics at the LUMC (head: Prof. dr. R.G.J. Westendorp). The position was embedded within an Innovation Oriented Research Program (IOP) entitled "The genetic determination of longevity and disease at old age" in which biologists, geneticists and physicians collaborated. The present thesis focuses on the human branch of this project. During this period the author was co-founder and chairman of the Genomics Network for Young Scientists (GeNeYouS).

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The author lives together with his girlfriend Femke Peters and their sons Kasper (2003) and Wiebe (2007).