Possible Associations between Successful Aging and Polymorphic Markers in the Werner Gene Region

MARI SILD,[a] CEMILE KOCA,[a] METTE H. BENDIXEN,[a] HENRIK FREDERIKSEN,[b] MATT McGUE,[b] STEEN KØLVRAA,[a] KAARE CHRISTENSEN,[b] AND BJØRN NEXØ[a]

[a]*Institute of Human Genetics, University of Aarhus, Aarhus, Denmark*

[b]*Institute of Public Health, University of Southern Denmark, Odense, Denmark*

ABSTRACT: Werner syndrome (WS) is an autosomal recessive segmental progeroid syndrome caused by mutations in the Werner (*WRN*) gene leading to the early onset of many (but not all) aspects of normal aging. To investigate whether the *WRN* gene affects the course of aging in non-Werner syndrome individuals, we performed association studies analyzing several single nucleotide polymorphisms (SNPs) in the *WRN* locus. We found certain close-set SNPs in the 5′ flanking region and 5′ UTR to be significantly associated with the cognitive functioning level in old age.

KEYWORDS: Werner syndrome; WRN; cognition; normal aging

Werner syndrome (WS) is a rare autosomal recessive disorder caused by mutations in the *WRN* gene.[1] Patients start developing premature aging symptoms such as graying of the hair, wrinkling of the skin, cataract, osteoporosis, and several age-related diseases after puberty and predominantly die before the age of 50 years.[2,3]

The exact molecular background of the WS remains vague, although the protein encoded by the *WRN* gene has been thoroughly investigated and found to exhibit helicase, DNA-dependent ATPase, and 3′-5′ exonuclease activities.[3,4] WS is associated with significantly increased genomic instability and transcriptional deficiencies. Studies of the WRN protein also indicate that it plays a role in DNA repair.[4,5]

As mutations in one gene result in so many aging-like phenotypic changes, it has been hypothesized that minor differences in the *WRN* gene function-

Address for correspondence: Mari Sild, Institute of Human Genetics, The Bartholin Building, Wilhelm Meyers Allé 240, Aarhus University, DK-8000 Aarhus C, Denmark. Voice: +45 8942 1631; fax: +45 8612 3178.
e-mail: sild@humgen.au.dk

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ing might contribute to the fact that the normal aging process differs among individuals.[6] To investigate this, we analyzed various SNPs in the *WRN* locus for possible associations with various indicators of normal aging, considering physical and cognitive factors as well as the occurrence of usual age-associated diseases. The DNA samples and personal data from 426 participants were obtained from the Danish Database of Ageing Twins (Longitudinal Study of Ageing Danish Twins) and genotyping was done with the Roche LightCycler real-time polymer chain reaction instrument.

To our surprise we found significant association values among the three SNPs in noncoding areas of the *WRN* gene (5′ UTR and 5′ flanking area) and a parameter of normal aging–cognitive functioning level as measured by a cognitive composite score.[7] The SNPs rs2251621, rs2725335, and rs2725338 demonstrated *P* values of 0.003, 0.004, and 0.001, respectively. Interestingly, mental impairment is not a typical WS feature.

In addition, three other SNPs (one in an exon) appeared to be associated with another parameter, "grip strength," with *P* values of 0.038, 0.005, and 0.003.

These SNPs might be located in or be in linkage disequilibrium with the yet undefined gene expression regulatory areas. We continue with haplotype studies and functional research.

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